INFLUENCE OF DIAZEPAM ON NEUROMUSCULAR BLOCKADE BY MUSCLE RELAXANTS

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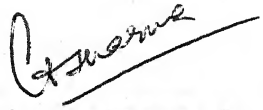
C E R T I F I C A T E

This is to certify that the work related to "INFLUENCE OF DIAZEPAM ON THE NEUROMUSCULAR BLOCKADE BY MUSCLE RELAXANTS", which is being submitted for the M.D. (Anaesthesiology)thesis was done by Dr. Mukesh Kumar Garg under my personal supervision and guidance. The techniques and methods described were undertaken by the candidate himself and the observations recorded have been periodically checked by me.

GUIDE



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A C K N O W L E D G E M E N T S

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Dated :

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INTRODUCTION

INTRODUCTION

Fighting disease with drugs is an ageless phenomenon. Its begining can be guessed as being as old as the history of man. Man's survival on this planet has depended largely upon alleviation of his sufferings by drugs. Till today the struggle continues in laboratory and clinic for the search of better and safer drugs for the welfare of the mankind. With the introduction of a large number of drugsin last half century, a new problem of significant dimensions has cropped up in the form of interaction of various drugs with each other.

"Drug interactions form part of the normal medical practice"(Dodson).

Interactions between drugs have been observed for a better part of a century and have been described under the classical headings of antagonism, synergism and potentiation. The spectrum of drug interactions is very wide. At one end there are useful and usually undramatic drug interactions like use of atropine in organophosphorus poisoning, potentiation of action of succinylcholine by procaine and propenidid (Torda et al., 1972). At the other

hand of the spectrum are dramatic and dangerous drug interactions, such as the profound hypotension, which occurs in some patients on antihypertensive drugs if given halothane or the fatal effects of pethidine given to patients on monoamine oxidase inhibitors.

Interactions between the therapeutically administered drugs can be a significant factor in determining clinical response to drug therapy. Unlike genetic or pathological factors which may influence a patient's response to medications, drug interactions are usually the direct result of physician's therapeutic decision, and thus, the adverse clinical consequences of drug interactions are potentially preventable (Cohen and Armstrong, 1974).

The days are gone when anaesthesia was administered with single anaesthetic agent like chloroform or ether. Now the anaesthesiologist is exposed to a plethora of anaesthetic and non-anaesthetic drugs, increasing the frequency of patient being given many other drugs in the operative or pre/post operative period, which might not be related to anaesthesia, but able to profoundly alter the patient's response to drugs given during or following surgery. The anaesthesiologist in particular makes use of many interactions, an

example being the use of neostigmine to reverse the action of non-depolarizing muscle relaxants.

Interactions involving commonly used drugs or potentially interacting drugs which are often likely to be given together are of more importance than those involving drugs that are infrequently used (Avery, 1976). Now a days diazepam has become one of the most commonly prescribed drug in the medical practice increasing the possibility of patient's taking it as advised by medical practioner or on his own, when he/she is proposed to undergo anaesthesia for any surgical operation. Apart from this, diazepam is usually also given on the night prior to surgery for the sound sleep and included in premedication to allay anxiety, apprehension and tension. It is used for the induction of anaesthesia also.

Besides being used as a tranquilliser it has also been found to be beneficial in relieving the skeletal muscle spasm in tetanus (Feni-Pearse, 1966; Hendrickse and Sherman, 1966), stiffman syndrome (Howard, 1963) and cerebral palsied children (Marsh, 1965).

The advent of neuromuscular blocking agents has made it possible for surgeons to perform the operations that they had never dreamt they would ever be able to. The neuromuscular blocking agents have been in clinical use for over three decades. They produce muscle relaxation in relatively light but adequate planes of general anaesthesia increasing the ease and efficiency with which the surgery is performed.

The key role of neuromuscular blocking agents in this field and the wide use of diazepam can prove to be a promising drug interaction. There is much controversy in the literature regarding the effect of diazepam on the neuromuscular blockade produced by depolarising and non-depolarizing skeletal muscle relaxants. Stovner and Endresen (1965), in their first clinical study indicated that diazepam did not significantly potentiate the action of d-tubocurarine or succinylcholine during abdominal operations. Later it was more emphatically suggested by Feldman and Crowley (1970 a, b) that diazepam increased the action of gallamine and decreased the duration of succinylcholine activity. It was observed by Lorenzo and Madiavilla (1973) that the commercially available solution of diazepam

enhanced the recovery from the blockade caused by d-tubocurarine in the cat but increased the recovery time of succinylcholine blockade.

There is still no definite opinion regarding the influence of diazepam on the neuromuscular blockade produced by muscle relaxants inspiring to undertake a study to resolve these conflicts.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Muscle relaxants, whether used in the jungle as poison for hunting animals or in the operation room, have always seemed highly dramatic and uniquely interesting. The pharmacologic nature of these drugs invites investigations, their sudden effectiveness commands respect, and their clinical application arouses continuing debate.

Neuromuscular transmission

Transmission from nerve to muscle is a process which begins with the synthesis and storage of acetylcholine inside motor - nerve terminals, from which the transmitter is released by nerve impulses. On arrival at the postjunctional (muscle) membrane, acetylcholine combines reversibly with receptor molecules ; as a result, an increase in membrane permeability brings about a transient depolarization at the end-plate (the end plate potential). The resulting ionic currents flowing across the adjecent muscle membrane are sufficiently intense to depolarize beyond the threshold and so initiate an action potential ; this in turn rapidly invades the whole of the muscle membrane and activates the contractile mechanism (Roberts and Gray, 1980)

The neuromuscular block may be produced at any one of the several stages in the process of transmission from nerve to muscle. In practice, however, neuromuscular block is usually achieved by modifying the activity of postjunctional (muscle) membrane in any one of the two ways.

Non - depolarizing block

This type of block is produced by drug that, while possessing sufficient affinity for the receptors to combine reversibly with them, does not bring about the changes in membrane permeability which underlie the end-plate potential. Therefore, acetylcholine competes with this drug for occupancy of receptor sites, as only a few are available so the end-plate potential is small. Neuromuscular block occurs when the end-plate potential fails to reach the threshold value and lasts as long as the concentration of this drug is high enough to compete effectively with acetylcholine. Examples are tubocurarine, gallamine and pancuronium.

Depolarising block

The depolarising drugs cause depolarisation of the end-plate. Then follows a period of block due

to the reduction in membrane potential of the electrically excitable muscle membrane around the end-plate. This reduction in membrane potential is due to persistent current flow from the end - plate region and it prevents the development of further electrical activity in mucle fibres by inactivating the normal relation between membrane potential and sodium permeability, which is the basis of the all-or-none potential mechanism. The example is suxamethonium.

Tubocurarine

This is an alkaloid extracted from the tropical plant 'Chondrodendron tomentosum', growing near the upper reaches of Amazon. It has long been used by natives of South America as poison, and they transported it in bamboo tubes, hence the name tubocurarine (Atkinson et al, 1977). In 1942, Griffith and Johnson in Montreal introduced curare into anaesthesia.

Chemically it is a quaternary alkaloid, having an isoquinoline ring. Now a days the original formula of d-tubocurarine is thought to be incorrect and according to the new formula elucidated by Everett and coworkers (1970) this drug has only

one stable quaternary ammonium group. The structure of the other nitrogen ion will vary according to the pH of the media behaving more like a tertiary ammonium compound at an alkaline pH.

The decrease in plasma d-tubocurarine level occurs in three phases. In phase one distribution to extracellular fluid compartment and plasma proteins occurs. In phase two it is redistributed to non-specific d-tubocurarine receptors throughout the body and finally in phase three it is excreted in urine (Waits and Dillon, 1968). Biliary system offers an alternative pathway of metabolism.

Katz and Gissen (1967) found that the duration of action of d-tubocurarine was 14-48 min (mean 36 min). Waits and Dillon (1968) observed that duration of action of d-tubocurarine averaged 1.5 times longer than that of gallamine. McDowell and Clarke (1968) reported that both the duration of onset of action as well as the duration of action of d-tubocurarine were longer than pancuronium.

Katz and coworkers (1969) found different duration of action in patients of London and USAF hospital. The 90 percent recovery time at London was 27.1 $\pm$ 10.1 min and at USAF hospital 37 $\pm$ 15 min.

Bennett and coworkers (1972) reported its duration of action to be 42.1 ± 18.34 min. Laurence (1975) describes that its maximal action is attained in 4 min and action lasts about 30 min. Bhargava and Chatterjee (1977) concluded that its mean onset of action is 5.37 min and duration of action is 48.5 min. Atkinson and colleagues (1977) state that after the therapeutic doses of tubocurarine the muscular power returns in 15-50 min. According to Feldman (1978) recovery from complete limb musculature paralysis occurs in 30-50 min. Snow (1978) states that tubocurarine acts intravenously within 3 min and effect may last 30-40 min. Sheth and Sabnis (1982) reported that the time interval for onset of action was 252 ± 48 sec while the duration of action was 31.12 ± 11.60 min.

Gallamine triethiodide

Following the introduction of d-tubocurarine into clinical anaesthesia, pharmacologists throughout the world sought for synthetic drugs with a similar action. In 1947, Bovet, Depierre and Lestrange described the muscle relaxant properties of a synthetic product gallamine triethiodide. The effects of this relaxant in man were first described by Huguenard and Boue (1948) in France

and by Mushin and his colleagues (1949) in England.

Gallamine chemically is tri-(β-diethylaminoethoxy) - benzene triethiodide. It produces non-depolarizing neuromuscular block and is excreted by the kidneys.

Waits and Dillon (1968) observed that the duration and magnitude of the block produced by gallamine was dose dependent and its duration of action was shorter than tubocurarine.

Monks (1972) found that its onset of action is 2-4 min and duration of action is 20-30 min. Atkinson and coworkers (1977) observed that its effect lasts about 20 min. Feldman (1978) describes that its duration of action is between 20-35 min and therefore on a comparative basis shorter than that of d-tubocurarine. Snow (1978) found its effect to last about 20-40 min. According to Calvey and Wilson (1980) its speed of onset is greater than that of tubocurarine and its duration shorter.

Sheth and Sabnis (1982) stated that the onset of action of gallamine was 309.6 ± 65.4 sec and duration of action was 37.44 ± 12.13 min.

Pancuronium bromide

Pancuronium bromide was first synthesized in 1964 by Hewett and Savage. Duckett and coworker (1966) carried out the experimental studies with pancuronium and described its pharmacological properties. It was introduced into clinical anaesthesia by Baired and Reid in 1967.

Chemically it is 3 β, 16β- dipiperidine-5α -androstane-3α, 17 β-diol diacetate dimethobromide.

It produces non-depolarizing type of neuromuscular block.

Pancuronium is believed to be excreted mainly unchanged in the urine. It is partly metabolized by hepatic microsomal enzymes.

McDowall and Clarke (1969) found that onset as well as duration of action of pancuronium is shorter than d-tubocurarine. Dick and coworkers (1970) noted that its onset of action is 1.95 ± .07 min and duration of action 49.8 min. Katz (1971) found that it took 207 sec to abolish complete twitch response. Varma and Sharma (1971) observed that within 2 min amplitude of twitch decreased to 1-2 mm and duration of paralysis was 30-45 min.

Bhargava and Chatterjee (1977) observed onset of action to be 2.03 min and duration of action 51 min. Atkinson and coworkers (1977) found onset to be 2-3 min and duration 20-30 min. Vickers et al. (1978) state that duration of peripheral block varies from 30-40 min. Snow (1978) observed onset within 3 min and duration about 30-40 min.

According to Feldman (1978) the paresis produced by pancuronium lasts for about 25-40 min and "The duration of action of pancuronium could be described as lying midway between the shorter action of gallamine and longer duration of d-tubocurarine".

In 1982, Sheth and Sabnis found that the time interval for onset of action was 161.20 ± 38.60 sec and duration was 50.40 ± 15.47 min.

Succinylcholine

In 1906 Reid Hunt and Taveau first described the pharmacological actions of suxamethonium, but though they studied its effect on blood pressure

they failed to observe that it causes neuromuscular block, because they were using a previously curarised animal. The drug was first used in man as a neuromuscular blocking agent by Theseleff in Stockholm (1951) and by Mayrhofer and Hassfurther (1951) in Austria. Scurr (1951) described its use in Great Britain.

Suxamethonium is a synthetic bis-quaternary ammonium compound.

Suxamethonium is believed to act like acetycholine in man and to bring about a depolarization type of neuromuscular block.

Following an intravenous dose it rapidly undergoes enzymatic hydrolysis with plasma cholinesterase. In the absence of enzymatic process it is slowly metabolized by alkaline hydrolysis. A very small amount is excreted unchanged in urine (Feldman ,1978).

Crul and coworkers (1966) found that after intravenous injection of succinylcholine total recovery occurs in 7 min 41 sec. Katz and Ryan (1969) observed 90 percent return of twitch height in 14.6 min.

Katz and coworkers (1969) found that 90 percent recovery time was different in London and NewYork. In London it was 9.1 ± 2.9 min and in NewYork 14.6 ± 3.6 min. Atkinson and coworkers (1977) state that it causes muscular relaxation for 3-5 min and then it rapidly disappears. According to Snow (1978) relaxation results within 1 min and recovery is complete within 5-15 min. Feldman (1978) states that it causes respiratory paralysis for 2-4 min. Calvey and Wilson (1980) state its duration of action to be 4-6 min. Blitt and coworkers (1981) concluded that it causes disappearance of twitch within 82.3 ± 5.9 sec with a 90 percent recovery in 652 ± 63 sec.

DIAZEPAM :

In this historical evolution, man has been able to dominate the nature by means of his technological achievements, his knowledge and his inventions, attaining an increasing control over the world and its organization. As a result, his power over his fellow men has also increased, giving him more and more responsibility which leads, of necessity, to one existential problem: is the contemporary man, with all his power and knowledge, really happy ?

Technological progresshas brought him several rights and desires : health, better insight into future and greater control over his destiny, but despite all this he still suffers from insecurity and from all the new problems that he has to face, which in fact account for his imperfections and limitations that inevitably generate anxiety.

Man is seeking relief from pain, suffering and naturally anxiety. Thus all possible efforts are being made to find a solution for this anxiety. The search for the substances that are able to eliminate anxiety is one of the constant concerns of modern science, and, in this context, one of the turning points, has been the discovery of chemical agents known as benzodiazepines.

In the midfifties, when a new class of therapeutic agents, the tranquillizers were shown to have considerable clinical value Roch decided to initiate a programme concerned with the search for products of this type. The initial discovery and development was the synthesis of 1, 4-benzodiazepines (Stembach, 1980).

The first successful benzodiazepine, chlordiazepoxide, was developed by Stranbach's group at Roche Laboratories in the late 1950s and the tests in animals showed interesting results (Baldessarini, 1980). This stimulated further research. Diazepam was first synthesised by Stanbach in 1961. The first pharmacological and clinical studies with diazepam were reported by Randall and colleagues in the same year. In the early papers it was known as R o 5-2807 (Dundee and Wyant, 1977). Diazepam was introduced in the market near the end of 1963 under trade name of Valium (Starnbach, 1980). Much of the early work with the drug was carried out in continental Europe and was concerned with its uses in psychiatry.

Diazepam is widely used in anaesthesiology for premedication, as an induction agent and to assure a state of basal sedation allowing a series of diagnostic and therapeutic, medical and surgical procedures to be performed. Its success in the field of psychiatry, particularly in anxiety-tension states (Tenlen, 1962) may have been responsible for its use as preanaesthetic medication, especially following a favourable

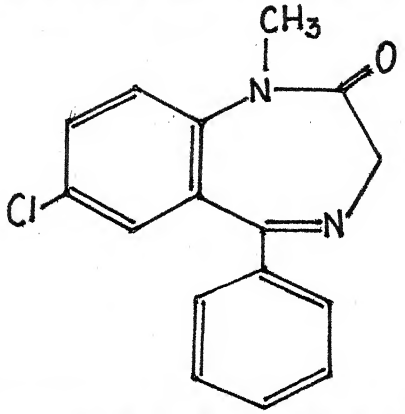
report on the use of the related compound chlordiazepoxide by Brandt and coworkers in 1962. In 1964 Aguado - Matorras and Aquerreta of France reported their experience with a combination of diazepam and dextromoramide in neuroleptanalgesia.

Further European studies by Campan and Espagno (1964), and Blondeau (1965b) suggested its value as an induction agent. The Scandinavian workers, Stovner and Endresen (1965a, b) were first to report its use as a sole agent for this purpose. It was studied in detail by a number of groups in Britain (Cushmen, 1966; Brown & Dundee, 1968).

Bapko and coworkers described the "Relief of the emotional factor in labour with parentrally administered diazepam" in 1965 and since then it has acquired increasing popularity in this field both as a sedative (Rouchy et al, 1966) and in the management of eclampsia (Lean et al, 1968).

Diazepam is now firmly established as a useful therapeutic agent in many fields.

Chemically diazepam is 7-chloro-1, 3-dihydro-1-methyl-5-phenyl-2H-1, 4-benzodiazepin-2-one. Its structure formula is



Diazepam is administered by oral, intramuscular and intravenous routes.

The peak effect of diazepam 10 mg intravenous comes in 2-5 min with duration of sedation 20-50 min and amnesia 3-30 min (Dundee, 1980). In a study conducted on twelve subjects Reized and Hailey (1972) reported that after 3 min a single 10 mg dose of diazepam produced a plasma level of 0.8 ± 0.21 microgram per ml. The subjects were relaxed, drowsy and unconcerned by the venous sample being taken, but all reacted to sample taken at 60 min. The initial clinical symptoms were repeated at 6 hr and 12 hr after intravenous injection. Enterohepatic cycle was thought to be the most probable cause for this.

The findings of Gamble and coworkers (1973) in relation to plasma levels of diazepam after intravenous administration coincide with that of Baird and Hailey (1972).

Benzodiazepines are drugs with a dose related tranquillizing-sedative-hypnotic action and with muscle relaxant and anticonvulsant properties (Dundee, 1980).

MUSCLE RELAXANT PROPERTY OF DIAZEPAM

CLINICAL STUDIES :

Campan and Espagno (1964) used diazepam in clinical anaesthesia, with dose upto 1 mg kg^{-1} in a continuous infusion (80 mg/250 ml). Since the intensity of the hypnotic action depended largely on the rate of infusion, effective dose had to be given in 5-8 min (approximately 10 mg min^{-1}). Anaesthesia was continued with nitrous oxide and various inhalational supplements alongwith intravenous opiates. They found that abdominal relaxation was adequate in about one third of their cases without curarizing agents. Recovery was not prolonged in any of their 200 patients.

In a pilot study on the muscle relaxant effect of diazepam during general anaesthesia, published in 1967, Hunter observed that out of 17 patients who received diazepam, in 4 patients 'adequate relaxation' was obtained with this drug as the only muscle relaxant and in these 4 cases no tubocurarine was required. However he stated that diazepam "produces some degree of relaxation of flat muscles of the abdominal wall, but the relaxation is insufficient for paramedian laparotomy".

Verzano and coworkers (1970) used diazepam in doses of 0.3 to 0.4 mg kg^{-1} intravenously in association with barbiturate and nitrous oxide. They found that muscle relaxation produced was sufficient to perform appendicectomy or inguinal herniorrhaphy.

Ludin and Dubach (1971) analysed the action of diazepam in 18 healthy subjects by studying the correlation between electromyographically recorded mean voltage and isometric tension in skeletal muscle. A significantly increased slope of voltage tension curves was found after giving diazepam, ie. the mean voltage at corresponding isometric tension was about 20 percent higher. The authors therefore conclude that this finding is probably due to an action of the compound on contractile mechanisms.

Hopf and Billmann (1973) studied in volunteers the effects of diazepam on skeletal muscle. Their results show a slight effect on the contractile mechanism and/or excitability of muscle membrane.

In 1979, Bradshaw and Maddison studied the effect of diazepam at the neuromuscular junction in patients undergoing surgery under general anaesthesia. All the patients were premedicated with diazepam not more than 10 mg orally. They found that diazepam in dose of 0.15 mg kg^{-1} had no effect on the mechanical twitch height of the adductor pollicis muscle of the thumb when the ulnar nerve was stimulated with single twitch or train of four.

EXPERIMENTAL STUDIES :

Diazepam has been claimed to be about 4 to 5 times as potent as chlordiazepoxide in muscle relaxant activity, as tested by the inclined-screen test and antistrychnine activity in mice, and gross muscular relaxation and spinal reflex activity in cats (Randall et al, 1961).

The effect of diazepam was studied upon the reflex and non-reflex contractions of tibialis anterior muscle of the chloralose anaesthetised cats by Hamilton (1967). He found that it was effective in blocking the reflex contraction of this muscle under these conditions and the primary muscle relaxant activity is central rather than peripheral. The same worker also conducted the experiments on the isolated rat phrenic nerve-diaphragm preparation and concluded that diazepam is capable of producing a dose related inhibition of both directly and indirectly elicited contractions.

Crankshaw and Raper (1968) studied the effects of diazepam on "in vivo" and"in vitro" nerve-muscle preparations. The "in vivo" preparation was a sciatic nerve-tibialis anterior muscle of chloralose-anaesthetised cat. The "in vitro" preparation was an isolated rat phrenic nerve-diaphragm preparation. It was found that although diazepam could abolish polysynaptic reflex contraction, but it has no peripheral effect on the response of skeletal muscle stimulated both indirectly (through nerve) and directly.

An experimental study in isolated frog muscle on the action of diazepam was conducted by Vergano and coworkers (1969). They found that the drug has outstanding muscle relaxant properties.

Dasgupta and coworkers (1969) have also reported a neuromuscular blocking effect of diazepam at the concentration of 40 µg per ml. They used two "in vitro" preparations (rat phrenic nerve-diaphragm and frog sciatic nerve-gastrocnemius). This effect could not be antagonised by physostigmine. At this concentration, the authors also found a slight reduction in the response to direct muscle stimulation.

In an experiment conducted by Vergano and coworkers (1970) with isolated frog sciatic nerve-gastrocnemius preparation diazepam alone produced transient reduction in twitch height. Prostigmine appeared to potentiate the relaxant effects of diazepam.

Experimental studies were conducted in various nerve muscle preparations by Dretchen and coworkers in 1971. They observed that diazepam, when given alone, did block the contractions of the isolated chick biventer cervicis nerve-muscle

preparation and the block was dose related. The actions of exogenously applied acetylcholine and nicotine were blocked by diazepam. The solvent system for the diazepam did not affect the twitch height or the exogenously applied drugs. The diazepam given intra-arterially in the dose of 5 mg also blocked contractions of dog anterior tibialis muscle and cat sciatic nerve-gastrocnemius muscle preparation.

Webb and Bradshaw (1973) found that diazepam, in doses of 0.2-5 mg kg^{-1} i.v.was without any effect on the maximal twitch response of the flexor hallucis longus or soleus muscle of the cat.

Blaber (1975) using rat phrenic nerve-diaphragm preparation, also found a neuromuscular blocking effect of diazepam, when used at a concentration of 70 µg/ml. He showed that the results were influenced by the chemical composition of the solution used.

Jain, Pandey and De (1976) while conducting the experiments with tibialis anterior sciatic nerve preparation of dogs concluded that

diazepam, in doses of 1 mg kg^{-1}, produces no effect on the response of tibialis anterior muscle to indirect stimulation.

In 1979, Walker and coworkers observed that diazepam (valium/Roche) caused an immediate cessation of spontaneous contractions in chick embryo skeletal muscle fibres growing "in vitro". They found that between 24-48 hours later in the presence of 100 μM diazepam the relaxed muscle fibres no longer accumulate myosin synthesis.

SITE OF ACTION :

A number of studies have imparted the knowledge of muscle relaxant property of diazepam. Various probable sites of action and mechanisms of action have been suggested to explain this property of diazepam, still, no conclusion has been reached regarding this.

Randall and coworkers (1961) suggested the supraspinal structures, such as the reticular activating system and polysynaptic pathways in spinal cord, as the probable sites of action accounting for muscle relaxation produced by diazepam.

In 1966 Ngai, Tseng and Wang studied the effect of diazepam and other central nervous system depressants on spinal reflexes in cats. They found that diazepam acts upon supraspinal structures, most likely the reticular facilitatory system, in blocking the spinal polysynaptic reflexes, the spinal cord itself appeared to be relatively resistant to depression by diazepam.

Hamilton (1967) reports that diazepam more readily inhibits the contractions due to rapid (60 min^{-1}) rather that slow rates of reflex stimulations, which is a central effect rather than a peripheral one on the myoneural junction. He further states that the experiments on the isolated rat phrenic nerve-diaphragm preparation have shown that these compounds are capable of an action at the peripheral neuromuscular synapse, although this is not the main site of action, but with higher doses and perhaps in certain pathological conditions this should be borne in mind.

In the same year, an interference with neuronal transmission at levels above the spinal cord was suggested by Parkes (1967).

Although diazepam abolishes polysynaptic reflex contraction, but it has no peripheral activity on skeletal muscle (Crankshaw and Raper, 1968).

Verzano and coworkers (1969) found that diazepam has outstanding muscle relaxant property but stated "their mechanism of action is still, in some respects, obscure".

Dundee and Haslett (1970) while reviewing the actions and uses of benzodiazepines concluded that although their antianxiety effect certainly contributes to the muscle relaxant action, part of it is due to a pharmacological action on polysynaptic pathway within the spinal cord or on supraspinal structures.

Feldman and Crawley (1970 a,b) concluded that diazepam acts by reducing the acetylcholine release at the presynaptic membrane.

In the same year, Hudson and Wolpert(1970) reported that diazepam acts primarily upon supraspinal structures. This view was shared by Nakanishi and Morris (1971).

Dretchen and Choneim (1971) although agree that central or supraspinal structures are the probable sites of action, yet they further suggest that diazepam also has an action at the neuromuscular synapse which may involve direct muscle depression.

Another view offered the contractile mechanisms of muscles as the probable site of action (Ludin and Dubach, 1971).

The results of Hopf and Billmann (1973) showed a slight effect on the contractile mechanisms and/or excitability of muscle membrane.

Webb and Bradshaw (1973) state "the unimpressive peripheral activity of diazepam on skeletal muscle under normal conditions emphasizes the importance of central sites, whether spinal or supraspinal to account for observed muscle relaxant activity in men and animals".

After reviewing the literature Martins (1975) concluded that diazepam acts at the different levels of the nervous system, not at the muscular end plate. Same view was expressed by Laurence(1975).

Bradshaw and Maddison (1979) excluded the possibility of neuromuscular junction as being the main site of action of diazepam, and accepted the supraspinal structures and polysynaptic pathways in spinal cord as the probable sites of action.

Diazepam has also been claimed to progressively inhibit the myosin synthesis in muscle fibres relaxed by it (Walker et.al, 1979).

Again in 1980, Dundee emphasized upon spinal cord as being the site of action of diazepam resulting in mild relaxation.

Uses of diazepam as muscle relaxant (outside anaesthesia) :

Diazepam, a benzodiazepine derivative, is effective both as a tranquillizer and for controlling the muscle rigidity and spasm of patients with various pathological conditions.

It has been found to be useful in the treatment of tetanus (Shershin & Katz, 1964 ; Femi-Pearse, 1966 ; Hendrickse and Sherman, 1966; Dundee and Haslett, 1970), stiff man syndrome (Howard, 1963 ; Olafson et al, 1964) and other

neurological disorders resulting in muscle rigidity and spasticity (Marsh, 1965 ; Nathan, 1970). Diazepam has been reported to improve patient's acceptability of positive pressure ventilation (Bozza-Marrubini and Selenati, 1973).

DRUG INTERACTION :

The first recorded anaesthetic death could have been prevented by a knowledge of drug interactions. Morbidity and mortality still continue our understandable ignorance of the subject. On the other hand, drug interactions have helped to transform the course of anaesthetic management, which currently relies on the skilled administration of several drugs to the same patient. Certainly combination therapy and drug interactions are the basis of "balanced" anaesthesia. Hence the art lies in the avoidence of hazardous interactions and in application of useful ones (Smith, 1981).

It is obvious that most therapeutically used interactions arise as a result of pharmacological knowledge of the drugs involved. On contrast, the majority of undesirable interactions are unpredicted, and experience precedes knowledge of the mechanism.

Occassionally, interactions are predicted, a good example being the prediction of the potentiation of succinylcholine by ecothiopate eye drops by McGavi in 1965, before the first case was described in 1966 (Gesztes, 1966 ; Pantuck, 1966).

A classification of drug interactions, on the basis of their mechanisms may aid in the prediction and thus prevention of those undesirable interactions, and suggest other therapeutically useful interactions. The drug interactions may be classified into :

1. Direct Interactions :

   A. Before drug administration : Caused by mixing of two drugs or a drug to an infusion fluid, eg. the precipitation occurs when thiopentone sodium and succinylcholine are mixed.

   B. In the body : Inactivation of heparin by protamine.

2. Interference with drug disposition :

   A. Absorption :

      The 'second gas' effect can be considered as a drug interaction. The alveolar concentration of one gas or vapour eg. halothane, increases

due to the administration of another gas such as nitrous oxide or ether.

B. Protein binding :

The metabolism of pethidine is reduced in patients taking oral contraceptives as the latter prevents the pethidine gaining access to the liver cells or its microsomes.

C. Metabolism :

The anticholinesterase drugs reverse the action of non-depolarizing muscle relaxants by inhibiting the metabolism of acetylcholine.

D. Excretion :

Chlorpropamide and salicylates compete for the same excretion pathway in the kidney, and when administered together, the hypoglycaemic effect may be increased (Stowers et al, 1959).

3. Interactions at the receptor site :

These include competitive interactions as well as interference at some part of the

pathway leading to the receptor site. Example being the potentiation of effects of neuromuscular blockers by several antibiotics like streptomycin, neomycin, kanamycin, gentamycin, polymyxin B and colistin.

Influence of diazepam on the neuromuscular blockade by muscle relaxants :

Diazepam is widely used in anaesthesiology for various purposes like premedication, induction of anaesthesia and basal sedation. Because of its marked muscle relaxant property it has always been a controversial point among anaesthesiologists and pharmacologists as to whether diazepam influences the effect of neuromuscular blocking agents.

In recent years, using different techniques and approaches, several workers have studied this and related questions in an attempt to clarify the problem and to elucidate the mechanisms of such an action. An amount of published material on this topic thus exists but, disappointingly enough, it sometimes shows conflicting results.

Clinical studies :

Blondeau (64, 65a, 65b) reported on his

experience with diazepam in general anaesthesia that the muscle relaxant effect remained slight but it did permit a considerable reduction in curarization if the latter was necessary.

In 1964, Joergensen using diazepam in a double blind trial (diazepam versus placebo) as premedication in a series of cholecystectomies, found a 10 percent reduction in the dosage of succinylcholine when 20 mg of diazepam had been given intramuscularly before the operation.

Stovner and Endresen, in 1965a, stated in a preliminary report on their experience with Valium® as an induction agent in anaesthesia that this preparation "did not significantly potentiate curarizing agents like tubocurarine, diallyl-nor-toxiferine (Alloferin®) or succinylcholine".

In the same year, Stovner and Endresen (1965b) stated in a paper read at Second European Congress of Anaesthesiology, in contrast to their previous article, that "the mean requirement of both diallyl-nor-toxiferine (Alloferin®) and tubocurarine during first hour of anaesthesia are about 8-10 percent lower when diazepam is used for induction compared to thiopentone".

Campan and Espagno (1966) found that when the diazepam was used the curariging agents could not always be dispensed with in abdominal surgery, but their dose on the whole was diminished.

A sparing effect of diazepam on the needs of peripheral muscle relaxant is mentioned without further details by Richter (1966) in relation to alcuronium.

Tonsa (1966) was unable to prove a succinylcholine - sparing effect of diazepam in comparison with thiopentone, despite the fact that diazepam considerably reduced the incidence of postoperative muscular pain caused by succinylcholine.

Cormier and coworkers (1966) found no difference in the requirements of tubocurarine between two groups of patients undergoing abdominal and gynaecological surgery and having received, as intramuscular premedication, diazepam (10 mg) or pethidine (100 mg).

Stevner and Endresen considered their previous findings hardly statistically significant because the number of patients were very few.

They made further studies in this field and published another article in 1969 and a paper together with Lund (1967), in which they observed that the mean requirement of muscle relaxants were about 10 percent lower when diazepam was used for induction compared to thiopentone. This finding proved to be statistically significant. The doses of diazepam used were between 15 to 25 mg.

A muscle relaxant sparing effect of diazepam on the needs of tubocurarine has been reported without further details by Toscani and Pasquali (1967).

Hunter (1967) concluded in a pilot study on the muscle relaxant effect of diazepam during general anaesthesia that the dose of tubocurarine needed to produce full muscular relaxation was substantially the same in a group of 9 patients who had received the diazepam and the another 13 who had during the same period been anaesthetized in exactly the same way but without this drug. However careful reading of this paper shows that in all diazepam was given to 17 patients and the above mentioned conclusion was based on data of nine patients only. In fact, in four other patients

adequate relaxation was obtained with diazepam as the only muscle relaxant and in these four cases tubocurarine was not required. Data from the remaining four patients concerning this specific point are not supplied. Diazepam was used in dosage of 2.5 to 10 mg in patients with an average weight of 71 kg.

Following a study involving three groups of patients and using three different anaesthetic procedures Vendramin and Luzzatto (1968) reported that there was an effective sparing of muscle relaxant when diazepam was used, both in respect of the classic barbiturate-succinylcholine anaesthesia and of neuroleptanalgesia combined with small doses of barbiturate.

Feldman and Crawley (1970a), while studying diazepam and muscle relaxants, observed that although diazepam had no effect on the twitch response to a supramaximal stimulus, it did however profoundly affect the action of muscle relaxants. After intravenous injection of 10 mg diazepam the neuromuscular block produced by the gallamine was increased about three folds both in degree and duration. The neuromuscular block produced by

succinylcholine was reduced following the same dose of diazepam. In the same year (1970b), they published another paper, in which they confirmed their previous conclusion. In this study they used diazepam in the doses of 0.15 to 0.20 mg kg^{-1}. The anaesthesia was maintained with nitrous oxide, oxygen and 0.5 to 1 percent halothane. They also reported that it was not possible to demonstrate a cumulative effect with diazepam if more than 15 min were allowed to elapse between the recovery from one dose of the drug and administration of the next.

More recently, Stovner and colleagues (1971) studied the influence of the induction agent (diazepam and thiopentone) on the requirements of gallamine and pancuronium in females undergoing lower abdominal surgery. They stated, "The doses (in mg sq m^{-1} of body surface) of these relaxants were 7-8 percent lower and displayed a lower inter-individual variation with diazepam compared with thiopentone".

Dretchen and coworkers (1971) did not find any alteration in recovery rate of any of the three neuromuscular blocking agents (d-tubocurarine,

gallamine and decamethonium) by the use of diazepam (in doses of 0.3 to 0.6 mg kg^{-1} intravenously) in human subjects.

After a comprehensive review of the literature on this subject, Martins (1975) concluded that diazepam slightly reduces the doses of neuromuscular blocking agents required during anaesthesia.

In their study of interaction of diazepam with non-depolarizing muscle relaxants Jain and coworkers (1976) found no significant changes in the mean time of onset of action, the mean intensity of action and mean 75 percent recovery time of d-tubocurarine (0.3 mg kg^{-1}) produced by diazepam 10 mg in human subjects.

In a clinical study conducted by Bradshaw and Maddison (1979), it was observed that diazepam 0.16 mg kg^{-1} had no effect on mechanical twitch height of adductor pollicis muscle of the thumb when the ulnar nerve was stimulated at the wrist. Further they concluded that diazepam in the same dose had no effect on the depth or recovery of neuromuscular blockade produced by suxamethonium, tubocurarine, pancuronium, fazadinium or alcuronium.

Dundee (1980) used diazepam extensively in anaesthesia. He commented that while the benzodiazepines have a mild muscle relaxant effect, their use during operation did not affect the requirement of myoneural blocking drugs.

Asbury and coworkers (1981) investigated the possibility of an interaction between diazepam and pancuronium in six patients undergoing general anaesthesia maintained with fentanyl, droperidol and nitrous oxide. Neuromuscular blockade was controlled using a feedback mechanism which automatically adjusted the rate of injection of pancuronium to maintain between 71.4 and 72.9 percent blockade. Diazepam 0.14 mg kg^{-1} intravenously produced blood concentrations within the therapeutic range, but did not produce consistant changes in the level of blockade, pancuronium concentration in the blood or pancuronium consumption measured over 20 min.

Experimental studies :

The effect of diazepam on neuromuscular blockade produced by muscle relaxants has also been studied on various animals.

Cheymol and coworkers (1967) observed, in rabbits, that diazepam potentiated the effects of tubocurarine and gallamine, but does not interfere with the effects of succinylcholine. In their studies these authors used the head drop method as well as an "in vitro" neuromuscular preparation (sciatic nerve-tibialis anterior muscle). The doses of diazepam that showed interaction with tubocurarine were twice as great as those showing interaction with gallamine. These authors also reported that diazepam, in high doses (10 mg kg^{-1}), increases the amplitude of the muscular contraction elicited by direct muscular stimulation.

Samsone and colleagues (1967) using the head drop method in the rabbit to study the interaction between tubocurarine and diazepam, arrived at results very similar to those of Cheymol and coworkers (1967) but with lower doses (0.166 mg kg^{-1}).

Mougdil and Pleuvry (1970) using "in vitro" neuromuscular preparation (rat phrenic nerve-diaphragm) did not observe any potentiation of the effects of either tubocurarine or gallamine

but reported an increase in the amplitude of contractions elicited by direct muscular stimulation.

It was reported by Vergano and coworkers (1970) that in isolated frog sciatic nerve - gastrocnemius preparation diazepam alone produced transient reduction in twitch height and in association with tubocurarine and gallamine muscle twitch was more markedly reduced than that produced by the drug alone and for longer duration.

Southgate and Wilson (1971), using an "in vivo" preparation (cat sciatic nerve - gastrocnemius muscle), failed to demonstrate any interaction between therapeutic doses of diazepam (intravenous) and either suxamethonium or gallamine.

In the same year Webb and Bradshaw (1971) while conducting experiments with cats failed to find any alteration in depth or time course of block produced by either gallamine or tubocurarine which could be contributed to diazepam (0.2 -0.4 mg kg^{-1}). In addition they found that diazepam in higher doses (1 mg kg^{-1}) enhanced the rate of

recovery from block without affecting the depth of block of either drug, but this weak effect was attributed to the solvent system of diazepam.

Dretchen and colleagues (1971) in addition to their studies in humans, also investigated the interaction of diazepam with neuromuscular blocking drugs in several animal nerve-muscle preparations. They concluded that the drug "did not alter the recovery slope of blockade produced by tubocurarine, decamethonium or gallamine. In low doses the commercially available drug given intra-arterially reversed the myoneural blockade produced by both depolarizing and non-depolarizing blockers. However, this property was due to the solvent system of the drug".

Lorenzo and Mediavilla (1973) reported that commercially available solution of diazepam enhanced the recovery from the blockade caused by d-tubocurarine in cat but increased the recovery time of the succinylcholine blockade.

In 1973, Webb and Bradshaw confirmed their previous findings and concluded that diazepam does not possess any prejunctional blocking activity.

Jain and coworkers (1976) found that diazepam in a bolus dose of 5 mg did not influence a pre-existing partial block by d-tubocurarine, gallamine or pancuronium. But a significant increase in both the degree and duration of block was observed when diazepam and d-tubocurarine were given simultaneously, suggesting an agonist action in diazepam. On the contrary simultaneous use of diazepam and gallamine caused a significantly less intense block of tibialis muscle twitch tensions as compared to gallamine alone, suggesting an antagonistic action.

In a study, conducted on sciatic nerve-gastrocnemium muscle preparation of dogs, Sharma and Sharma (1978) found that commercially available solution of diazepam (Calmpose®) significantly reversed the neuromuscular blockade produced by a non-depolarising agent like gallamine but augmented the blockade produced by a depolarizing agent like succinylcholine.

MATERIAL & METHOD

MATERIAL AND METHODS

This study was conducted on the patients presenting themselves for surgical operations at M.L.B. Medical College Hospital, Jhansi. The aims and objects of the study are :-

1- To assess the effect of diazepam on the neuromuscular blockade produced by depolarizing and non-depolarizing muscle relaxants viz succinylcholine, gallamine, pancuronium and tubocurarine respectively.

2- To assess the duration of action of blockade produced by succinylcholine, gallamine, pancuronium and tubocurarine.

3- To assess the neuromuscular blockade activity of diazepam, if any.

SELECTION OF CASES

Adult patients of both the sexes, scheduled for routine surgical operations, were included in the study. Preference was given to the cases undergoing surgical operations which

did not necessitate profound muscular relaxation. Each patient was subjected to a detailed history and clinical examination.

The following routine investigations were conducted :-

1- Haemoglobin estimation.

2- Total and differential leukocyte count.

3- Erythrocyte sedimentation rate.

4- Complete chemical and microscopic urine examination.

All the patients were in good physical state, without any neuromuscular disease and were not receiving any drug known to influence the action of neuromuscular blocking drugs. All the cases selected for the study belonged to ASA Grade I and II.

GROUPING OF THE PATIENTS

Patients were divided into two main groups, according to the time when the diazepam was administered. The proprietary preparation of diazepam used was 'Calmpose®', which has a composition as follows :

Each two ml of calmpose contains :-

Diazepam U.S.P. - 10 mg

Benzoic acid I.P. - 6 mg

Benzyl Alcohol I.P. - 0.03 ml

Sodium benzoate I.P. - 94 mg

Ethyl Alcohol I.P. - 0.2 ml

Propylene Glycol U.S.P.-0.8 ml

Water for injection q.s. 2 ml

It was administered in doses of 0.13 to 0.17 mg kg^{-1} body weight.

GROUP A :

Patients of this group received the diazepam intravenously 3-5 min before the dose of muscle relaxant which was to be studied in those particular patients.

GROUP B :

The patients of this group received the diazepam intravenously at the start of recovery from the muscle relaxant drug.

The patients of both the groups were further subdivided into four subgroups each

according to which one of the four muscle relaxants was given to them.

Subgroups A1 and B1 - Received succinylcholine.
Subgroups A2 and B2 - Received gallamine.
Subgroups A3 and B3 - Received pancuronium.
Subgroups A4 and B4 - Received tubocurarine.

All the patients served as control for themselves. This helped in minimizing the error arising due to the individual variation in response to muscle relaxant drugs.

The patients were prepared for general anaesthesia for routine surgery. Vitals were recorded before the administration of premedicant drugs.

TECHNIQUE OF ANAESTHESIA

I- PREMEDICATION :

The preanaesthetic medication consisted of atropine 0.65 mg and pethidine 1 mg kg^{-1}. Both the drugs were administered intramuscularly one hour before surgery.

II- INDUCTION :

An intravenous line was set up in a big vein and infusion of 5% Dextrose D/W was started.

All the subsequent drugs were given through this line.

After pre-oxygenation for five minutes induction was carried out by intravenous thiopentone sodium (Intraval® sodium) 2.5% in a dose sufficient to abolish the eyelash reflex (approximately 4-5 mg kg^{-1}).

III- INTUBATION :

Succinylcholine chloride (Scoline®) 1-1.5 mg kg^{-1} was administered intravenously to produce muscular relaxation for endotracheal intubation. After anaesthetising the larynx with 4% xylocaine, a cuffed endotracheal tube of appropriate size was passed into the trachea and connected to a non-rebreathing circuit and intermittent positive pressure ventilation instituted.

IV- MAINTENANCE OF ANAESTHESIA :

A non- rebreathing technique incorporating the Ruben non-rebreathing valve with high gas flow was used. The gas mixture consisted of nitrous oxide and oxygen in ratio of 6:4. Halothane was added to this mixture as and when needed.

As the twitch height in response to peripheral nerve stimulation attained the maximum magnitude the muscle relaxant (under study) was given intravenously in the following doses :

1.	Succinylcholine	0.94 to 1.11 mg kg^{-1}
2.	Gallamine	1 to 1.78 mg kg^{-1}
3.	Pancuronium	0.04 to 0.05 mg kg^{-1}
4.	Tubocurarine	0.13 to 0.25 mg kg^{-1}

After the return of twitch height to the basal level fifteen minutes were allowed to elapse before the same second intravenous dose of the same muscle relaxant to the same patient was given.

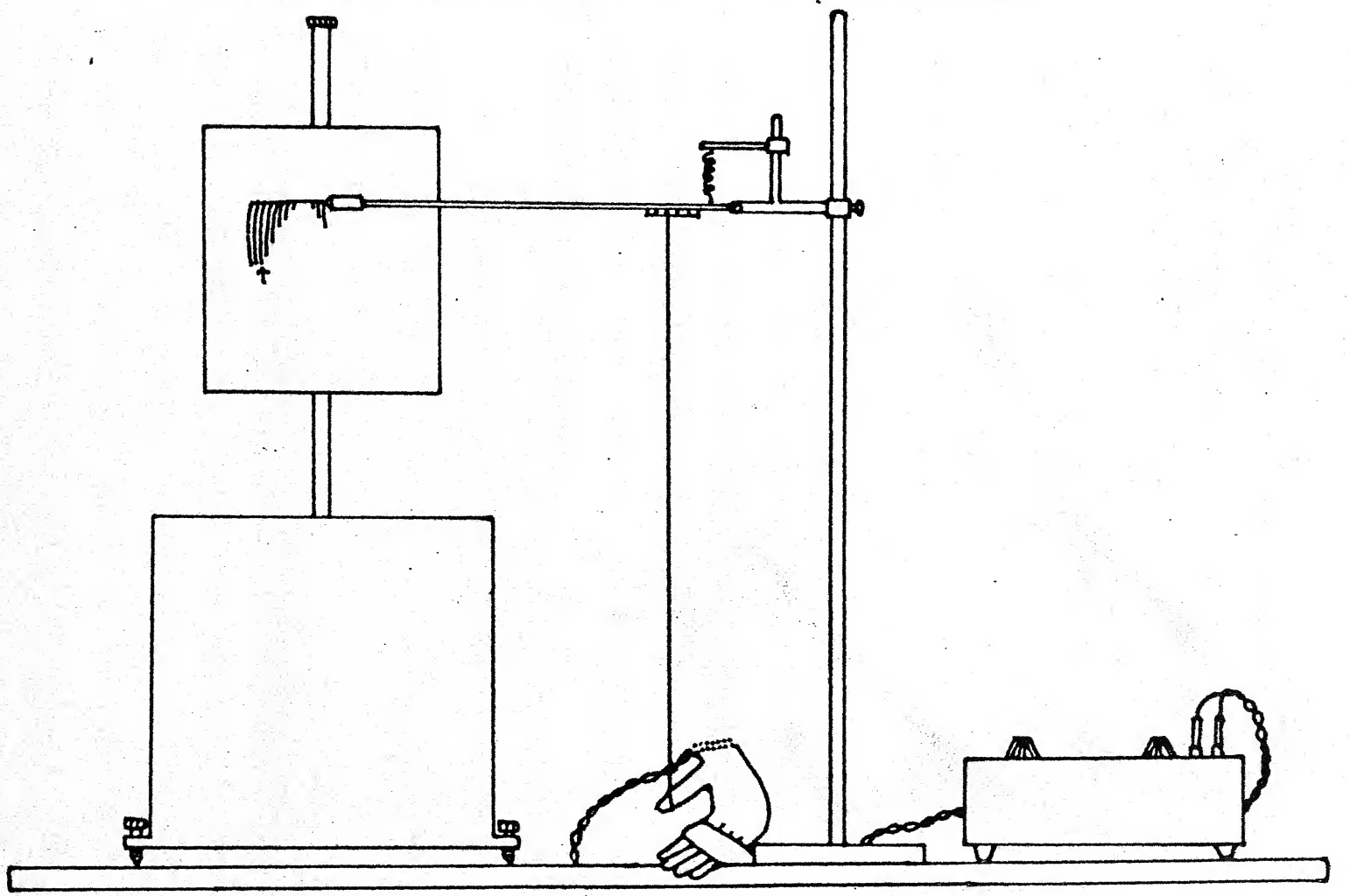
The first dose of muscle relaxant drug served as control for that particular patient while the effect of diazepam was observed on the second dose of that muscle relaxant.

MONITORING OF NEUROMUSCULAR BLOCKADE :

In the present study the recording technique used to monitor the neuromuscular blockade was a modification of the method described by Baraka (1964). Same technique was used by Verma and Sharma (1971) while studying pancuronium bromide.

APPARATUS USED FOR MONITORING OF NEUROMUSCULAR BLOCKADE

FIG 1



When the patient was placed on the operation table, the arm was extended laterally on an arm board and fixed to it by adhesive strappings. The hand was fixed in midprone position, immobilizing all the fingers except thumb to eliminate the error produced by movement of fingers other than the thumb.

The thumb was attached to an isometric writing lever by the help of a non-stretchable silk thread. No pulley or any other device was used in between the thumb and writing lever to eliminate any undue resistance affecting the recording of twitch height(Fig 1).

The writing lever recorded the twitch height in response to ulnar nerve stimulation on smoked paper mounted on kymograph.

Just after the induction of anaesthesia the skin over wrist of immobilized arm was cleaned with spirit. Two sterile 24 gauge steel hypodermic needles were placed subcutaneously 1-2 cm apart close to the lateral side of pisiform bone as the ulnar nerve passed along this course (Romanes,1973). These hypodermic needles served well as subcutaneous electrodes.

The ulnar nerve was stimulated using a Cinex nerve stimulater NS-2 with frequency of 0.1 Hz. The duration of each stimulus was 300 us and the intensity was adjusted in each case to get sufficient height of curve.

The maximum twitch height obtained prior to the injection of muscle relaxant under study served as basal recording. After the injection of muscle relaxant the maximum twitch suppression was considered as peak of action. The return of twitch height to the basal level was considered as the recovery from muscle relaxant drug.

With the help of above criteria the following parameters were measured using a stop watch.

I- Onset of action : It was measured from the last drops of injection of muscle relaxant to the attainment of peak of action.

II- Duration of action : It was measured from peak of action to the recovery from the given dose of muscle relaxant.

The recordings on the smoked paper were fixed by dipping it into 5% solution of shellac in methylated spirit.

REVERSAL :

At the end of surgical operation nitrous oxide was turned off and full oxygenation started. If a non-depolarizing muscle relaxant was used for study then it was followed by inj neostigmine 2.5 mg and inj atropine 1.2 mg. Both the drugs were given intravenously and very slowly. Then as the reflexes returned extubation was done. Patients were shifted out of operation theatre in full conscious state.

POST OPERATIVE :

The patients were watched for respiratory sufficiency and muscle strength.

OBSERVATION

O B S E R V A T I O N S

In the present work the influence of diazepam on the neuromuscular blockade by muscle relaxants was studied. To fulfill the purpose of the study it was approached in the following way :-

(A) Firstly the normal onset and duration of action of muscle relaxants along with twitch suppression produced by them were assessed. Total 62 cases were studied out of which 20 received succinylcholine (32.25%), 16 gallamine (25.81%), 16 pancuronium (25.81%) and 10 tubocurarine (16.13%) as shown in table 1.

TABLE NO. 1

Showing distribution of cases into different groups

S.No.	Muscle relaxant	No. of cases (%)
1.	Succinylcholine	20 (32.25%)
2.	Gallamine	16 (25.81%)
3.	Pancuronium	16 (25.81%)
4.	Tubocurarine	10 (16.13%)
	Total	62

(B) Secondly the onset and duration of action along with the twitch suppression produced by above mentioned muscle relaxants were assessed when these were used with diazepam. These values were compared with the normal values assessed in the same patients to see any influence of diazepam on them. For this purpose the cases were divided into various groups as shown in table 2.

TABLE NO. 2

Showing distribution of cases into various groups

S.No.	Muscle relaxant	Diazepam given before muscle relaxant No.	Diazepam given at the start of recovery No.	Total No. (%)
1.	Succinylcholine	10	10	20(32.25%)
2.	Gallamine	8	8	16(25.81%)
3.	Pancuronium	8	8	16(25.81%)
4.	Tubocurarine	5	5	10(16.13%)
	Total	31	31	62

(C) Thirdly it was assessed whether diazepam itself has some muscle relaxant property or not. It was done by observing its effect on twitch height in response to electrical stimulation (n = 31).

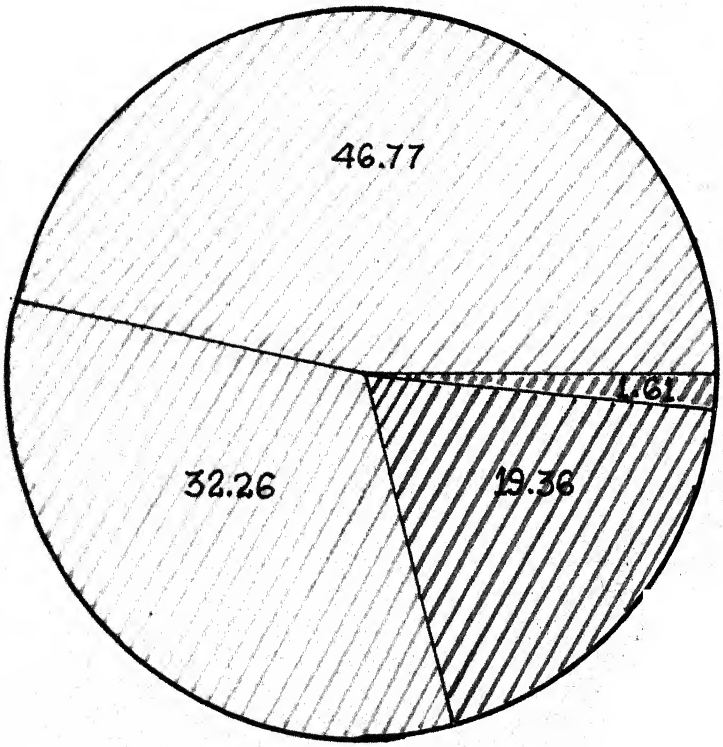
TABLE NO. 3

Showing type of surgery done

S.No.	Type of surgery	No. (%)
1.	General surgery	29 (46.77%)
2.	Orthopaedic surgery	20 (32.26%)
3.	Gynaecological and Obstetrical surgery	12 (19.36%)
4.	Ophthalmic surgery	1 (1.61%)
	Total	62

In the present study out of 62 cases, 29 cases underwent general surgery, 20 cases orthopaedic surgery, 12 cases gynaecological and obstetrical surgery and 1 case ophthalmic surgery (Fig 2).

Fig 2. PIE DIAGRAM SHOWING DISTRIBUTION OF VARIOUS TYPES OF SURGERY.



GENERAL SURGERY

ORTHOPAEDIC SURGERY

GYNAECOLOGICAL AND OBSTETRICAL SURGERY

OPHTHALMIC SURGERY

TABLE NO. 4

Showing age - distribution in patients

Age group (Years)	Succinylcholine No.	Gallamine No.	Pancuronium No.	Tubocurarine No.	Total No. (%)
16 - 20	5	3	1	4	13 (20.97%)
21 - 25	2	3	1	2	8 (12.90%)
26 - 30	1	1	3	1	6 (9.68%)
31 - 35	2	5	1	2	10 (16.13%)
36 - 40	4	2	4	1	11 (17.74%)
41 - 45	2	1	1	-	4 (6.45%)
46 - 50	2	1	5	-	8 (12.90%)
51 - 55	2	-	-	-	2 (3.23%)
Total	20	16	16	10	62

Mean age (± SEM) in 62 patients is 33.18 ± 1.40 years, in succinylcholine group 34.40 ± 2.72 years, in gallamine group 31.06 ± 2.38 years, in pancuronium group 38.38 ± 2.55 years and in tubocurarine group 25.80 ± 2.55 years.

TABLE NO. 5

Showing weight distribution in the patients

Weight of the patients (Kg)	Succinylcholine No.	Gallamine No.	Pancuronium No.	Tubocurarine No.	Total No. (%)
26 - 30	-	1	-	1	2 (3.23%)
31 - 35	1	-	2	1	4 (6.45%)
36 - 40	6	7	1	3	17 (27.42%)
41 - 45	2	2	4	1	9 (14.51%)
46- 50	9	2	6	3	20 (32.26%)
51 - 55	2	1	3	1	7 (11.29%)
56 - 60	-	3	-	-	3 (4.84%)

Mean weight ($\pm$ SEM) in 62 patients is 45.48 $\pm$ 0.89Kgin succinylcholine group 45.80 $\pm$ 1.23 Kg, in gallamine group 45.38 $\pm$ 2.26 Kg, in pancuronium group 46.81 $\pm$ 1.55 Kg and in tubocurarine group 42.90 $\pm$ 2.40 Kg.

Showing sex - distribution in patients

Sex of the patient	Succinylcholine No. (%)	Gallamine No. (%)	Pancuronium No. (%)	Tubocurarine No. (%)	Total No. (%)
Male	10 (50%)	7 (43.75%)	8 (50%)	4 (40%)	29 (46.77%)
Female	10 (50%)	9 (56.25%)	8 (50%)	6 (60%)	33 (53.23%)
Total	20	16	16	10	62

TABLE NO. 7

Showing distribution of ASA grading in patients

ASA Grade	Succinylcholine No. (%)	Gallamine No. (%)	Pancuronium No. (%)	Tubocurarine No. (%)	Total No. (%)
ASA grade I	13 (65%)	7 (43.75%)	4 (25%)	6 (60%)	30 (48.39%)
ASA grade II	7 (35%)	9 (56.25%)	12 (75%)	4 (40%)	32 (51.61%)
Total	20	16	16	10	62

TABLE NO. 8

Showing comparison of onset of action of muscle relaxants

Onset of action (sec)	Succinylcholine No.	Gallamine No.	Pancuronium No.	Tubocurarine No.
0 - 30	2	-	-	-
31 - 60	14	-	-	-
61 - 90	4	-	1	-
91 - 120	-	3	8	-
121 - 150	-	7	4	-
151 - 180	-	4	3	2
181 - 210	-	2	-	2
211 - 240	-	-	-	4
241 - 270	-	-	-	2
Total	20	16	16	10

The mean onset of action (± SEM) of succinylcholine is 54 ± 3.51 sec. In non-depolarising muscle relaxants pancuronium has the shortest (128.75 ± 6.89 sec) and tubocurarine longest (218 ± 9.17 sec) onset of action with gallamine in between (152.5 ± 6.42 sec). The difference between onset of action of gallamine and pancuronium is significant ($P < 0.05$) while it is highly significant between tubocurarine and gallamine ($P < 0.01$) and tubocurarine and pancuronium ($P < 0.01$) (Fig 3).

Fig 3. COMPARISON OF ONSET OF ACTION OF MUSCLE RELAXANTS

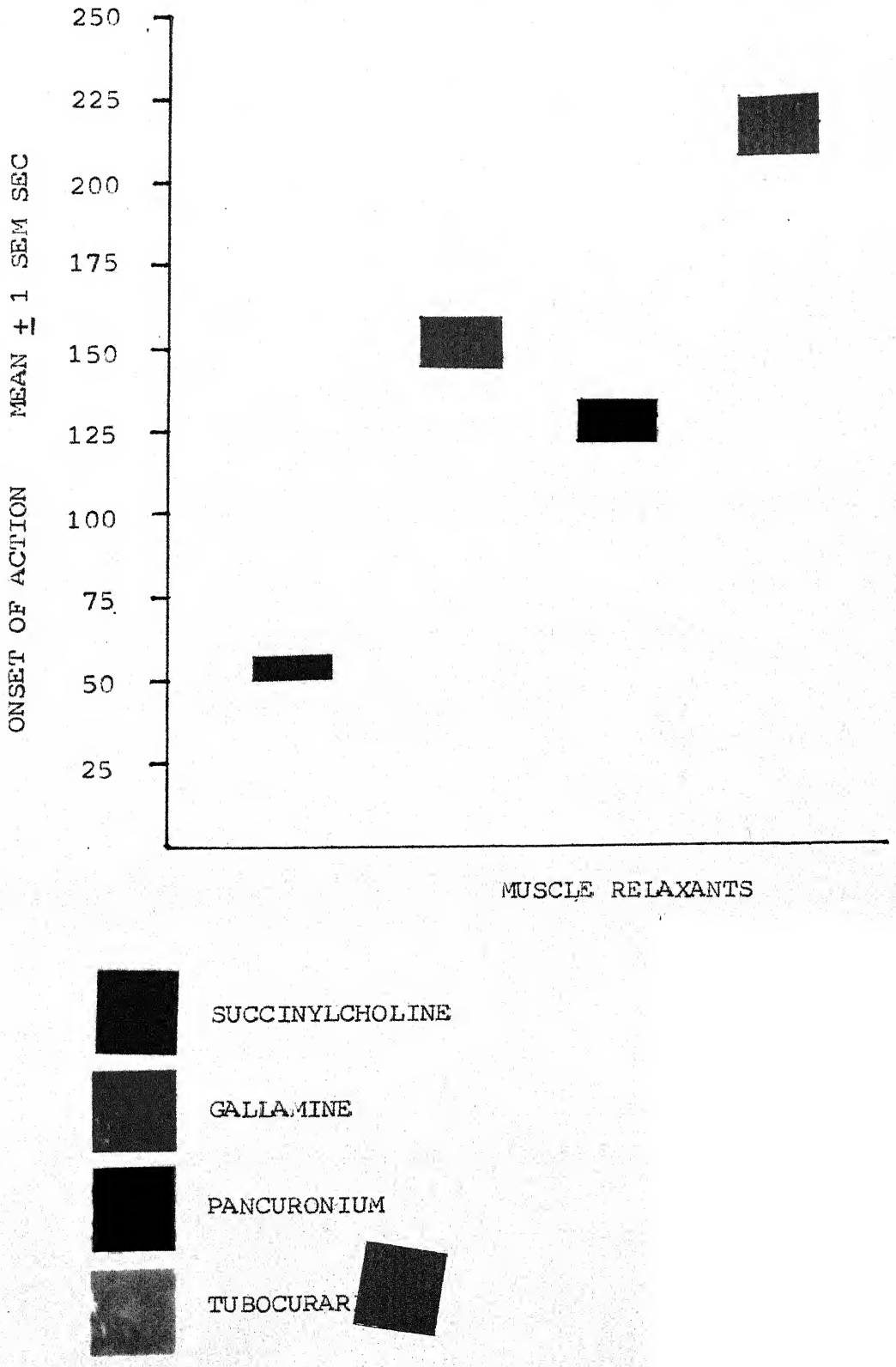


TABLE NO. 9

Showing comparison of duration of action of muscle relaxants

Duration of action (min)	Succinylcholine No.	Gallamine No.	Pancuronium No.	Tubocurarine No.
5.1- 10	18	-	-	-
10.1 - 15	2	-	-	-
15.1 - 20	-	-	-	-
20.1 - 25	-	3	1	-
25.1 - 30	-	5	1	-
30.1 - 35	-	2	5	2
35.1 - 40	-	5	9	-
40.1 - 45	-	1	-	-
45.1 - 50	-	-	-	3
50.1 - 55	-	-	-	5
Total	20	16	16	10

The mean duration of action (± SEM) of succinylcholine is 7.61 ± 0.45 min. In non-depolarising muscle relaxants gallamine has the shortest (31.43 ± 1.55 min) and tubocurarine the longest (46.87 ± 2.52 min) duration of action with pancuronium in between (34.46 ± 1.13 min). The difference between duration of action of gallamine and pancuronium is statistically insignificant while it is highly significant between tubocurarine and gallamine ($P < 0.01$) and tubocurarine and pancuronium ($P < 0.01$) (Fig 4).

Fig 4. COMPARISON OF DURATION OF ACTION OF MUSCLE RELAXANTS

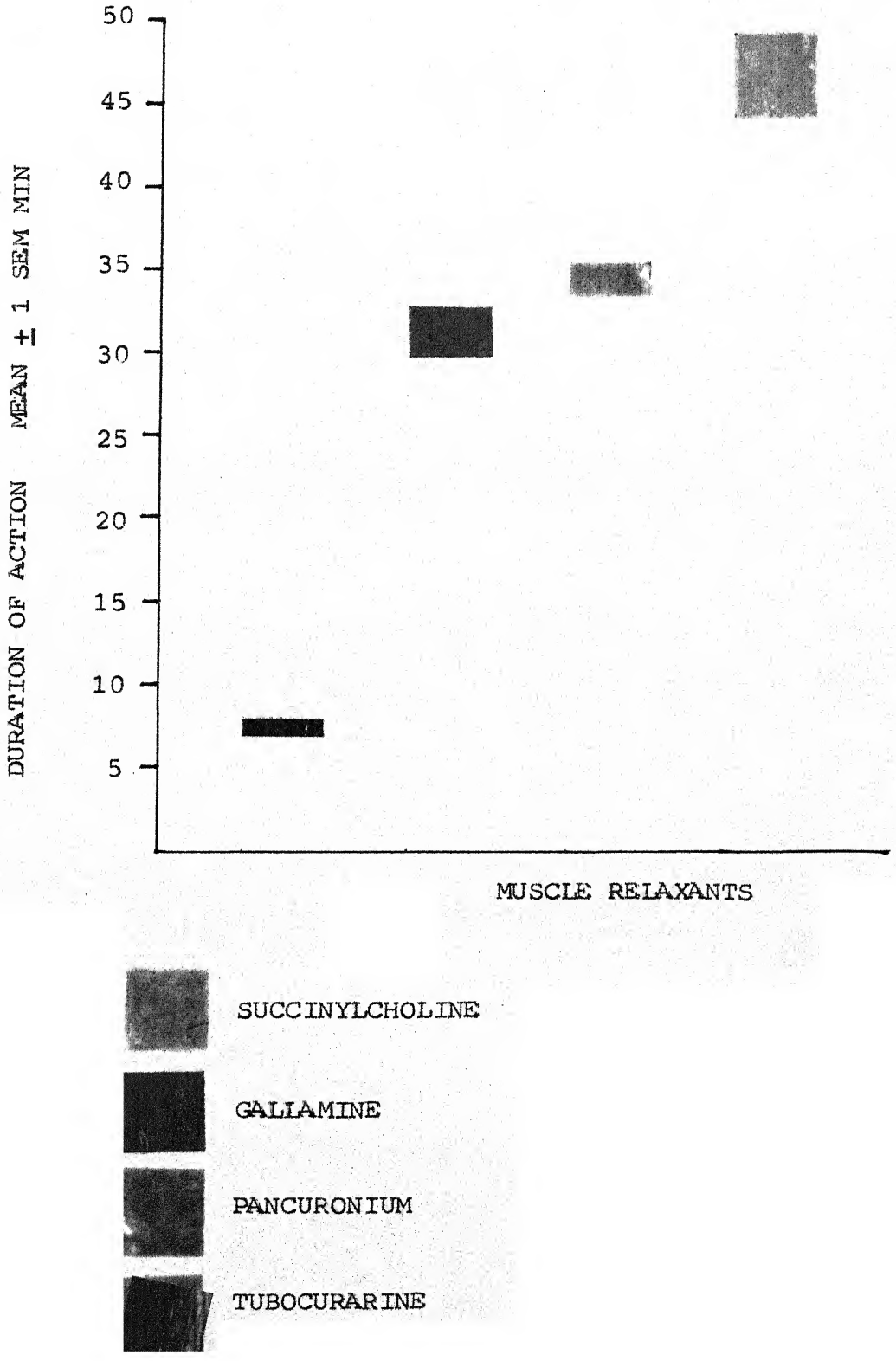


TABLE NO. 10

Showing the comparison of twitch suppression produced by muscle relaxants

Twitch suppression in %	Succinylcholine No.	Gallamine No.	Pancuronium No.	Tubocurarine No.
31 - 40	-	2	-	-
41 - 50	-	3	3	3
51 - 60	-	3	4	1
61 - 70	-	-	1	-
71 - 80	-	1	1	1
81 - 90	-	1	2	2
91 -100	20	6	5	3
Total	20	16	16	10

The difference between the mean (± SEM) twitch suppression produced by non - depolarizing muscle relaxants i.e. gallamine (73.13 ± 6.17%) - pancuronium (75.63 ± 5.02%) - tubocurarine (76 ± 9.97%) are not statistically significant (Fig 5).

Fig 5. COMPARISON OF TWITCH SUPPRESSION PRODUCED BY MUSCLE RELAXANTS

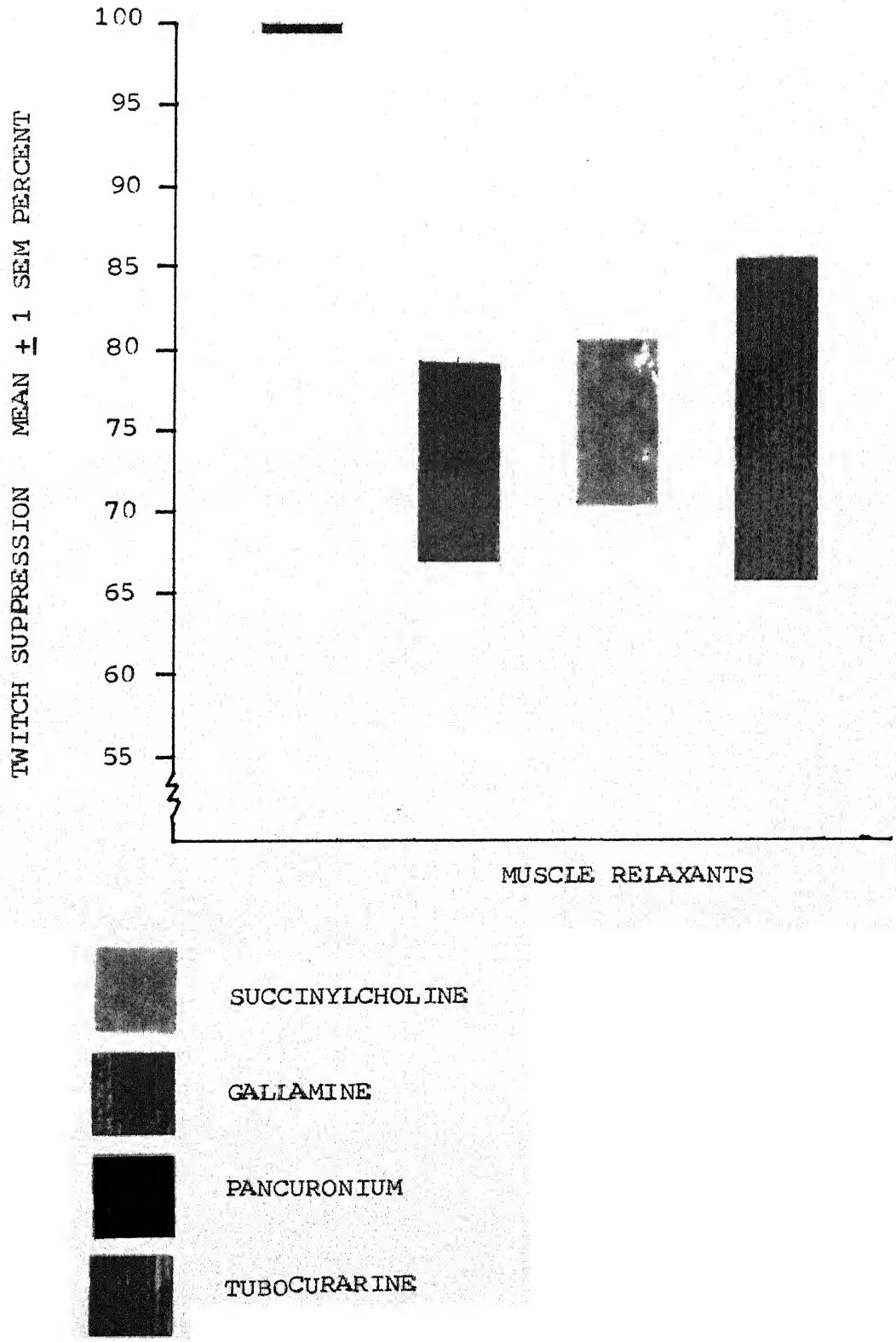


TABLE NO. 11

Showing comparison of various parameters of muscle relaxant groups

S.No.	Parameter	Succinylcholine	Gallamine	Pancuronium	Tubocurarine
1.	No.of cases (%)	20 (32.25%)	16 (25.81%)	16 (25.81%)	10 (16.13%)
2.	Age in years Mean ± SEM	34.40 ± 2.72	31.06 ± 2.38	38.38 ± 2.55	25.80 ± 2.55
3.	Sex distribution				
	- Male No. (%)	10 (50%)	7 (43.75%)	8 (50%)	4 (40%)
	- Female No. (%)	10 (50%)	9 (56.25%)	8 (50%)	6 (60%)
4.	Weight in kg Mean ± SEM	45.80 ± 1.23	45.38 ± 2.26	46.81 ± 1.55	42.90 ± 2.40
5.	ASA Grade				
	- ASA I No. (%)	13 (65%)	7 (43.75%)	4 (25%)	6 (60%)
	- ASA II No. (%)	7 (35%)	9 (56.25%)	12 (75%)	4 (40%)
6.	Onset of action in sec Mean ± SEM	54 ± 3.51	152.5 ± 6.42	128.75 ± 6.89	218 ± 9.17
7.	Duration of action in min. Mean ± SEM	7.61 ± 0.45	31.43 ± 1.55	34.46 ± 1.13	46.87 ± 2.52
8.	Twitch suppression in %. Mean ± SEM	100 ± 0	73.13 ± 6.47	75.63 ± 5.09	76.00 ± 9.97

TABLE NO. 12

Showing comparison of onset of action of muscle relaxants with and without diazepam (Diazepam given 3-5 min before muscle relaxant).

Sl. No.	Muscle relaxant	Onset of action without diazepam Mean ± SEM sec	Onset of action with diazepam Mean ± SEM sec	Significance
1.	Succinylcholine	57 ± 5.98	50 ± 4.72	Not significant
2.	Gallamine	151.25 ± 12.01	177.5 ± 10.97	Not significant
3.	Pancuronium	126.25 ± 5.95	128.75 ± 5.49	Not significant
4.	Tubocurarine	208 ± 14.94	230 ± 14.81	Not significant

The difference between the onset of action, with and without diazepam, is statistically not significant in any of the four muscle relaxants.

TABLE NO. 13

Showing comparison of onset of action of muscle relaxants with and without diazepam (Diazepam given at the start of recovery).

Sl. No.	Muscle relaxant	Onset of action without diazepam Mean ± SEM sec	Onset of action with diazepam Mean ± SEM sec	Significance
1.	Succinylcholine	51.00 ± 3.79	49.00 ± 2.34	Not significant
2.	Gallamine	153.75 ± 5.65	160.00 ± 7.07	Not significant
3.	Pancuronium	131.25 ± 12.87	132.50 ± 12.20	Not significant
4.	Tubocurarine	229.00 ± 10.18	242.00 ± 7.33	Not significant

There is no statistically significant difference between the onset of action, with and without diazepam, in any of the four muscle relaxants.

TABLE NO. 14

Showing comparison of duration of action of muscle relaxants with and without diazepam (Diazepam given 3-5 min before muscle relaxant).

Sl. No.	Muscle relaxant	Duration of action without diazepam Mean ± SEM min	Duration of action with diazepam Mean ± SEM min	Significance
1.	Succinylcholine	7.70 ± 0.44	7.01 ± 0.41	Not significant
2.	Gallamine	30.66 ± 2.43	45.06 ± 4.68	P 0.05
3.	Pancuronium	34.29 ± 1.48	56.60 ± 2.97	P 0.01
4.	Tubocurarine	46.54 ± 3.56	65.17 ± 3.99	P 0.01

There is no statistically significant difference in mean duration of action of succinylcholine with and without diazepam. With diazepam there is a significant increase in the mean duration of action of gallamine by 46.97% (P 0.05). Pancuronium by 65.06% (P 0.01) and tubocurarine by 40.03% (P 0.01).

TABLE NO. 15

Showing comparison of duration of action of muscle relaxants with and without diazepam (Diazepam given at the start of recovery).

Sl. No.	Muscle relaxant	Duration of action without diazepam Mean ± SEM min	Duration of action with diazepam Mean ± SEM min	Significance
1.	Succinylcholine	7.51 ± 0.80	6.68 ± 0.50	Not significant
2.	Gallamine	32.19 ± 2.04	49.08 ± 2.07	P 0.01
3.	Pancuronium	34.62 ± 1.79	49.66 ± 3.83	P 0.01
4.	Tubocurarine	47.20 ± 3.96	63.73 ± 2.72	P 0.01

The difference in mean duration ofaction of succinylcholine with and without diazepam is statistically insignificant. But with diazepam there is a significant increase in the mean duration of action of gallamine by 52.47% (P 0.01), Pancuronium by 43.44% (P 0.01) and tubocurarine by 35.02% (P 0.01).

TABLE NO. 16

Showing comparison of twitch suppression produced by muscle relaxants with and without diazepam (Diazepam given 3-5 min before muscle relaxant).

Sl. No.	Muscle relaxant	Twitch suppression without diazepam Mean ± SEM %	Twitch suppression with diazepam Mean ± SEM %	Significance
1.	Succinylcholine	100.00 ± 0.00	100.00 ± 0.00	-
2.	Gallamine	71.88 ± 9.25	94.37 ± 4.37	P 0.05
3.	Pancuronium	76.87 ± 8.39	98.12 ± 1.31	P 0.01
4.	Tubocurarine	77.00 ±12.18	99.00 ± 1.00	P 0.01

In non-depolarising muscle relaxants there was a significant increase in the mean twitch suppression after administration of diazepam. It was 31.29% in gallamine group (P 0.05), 27.64% in pancuronium group (P 0.01) and 28.57% in tubocurarine group (P 0.01).

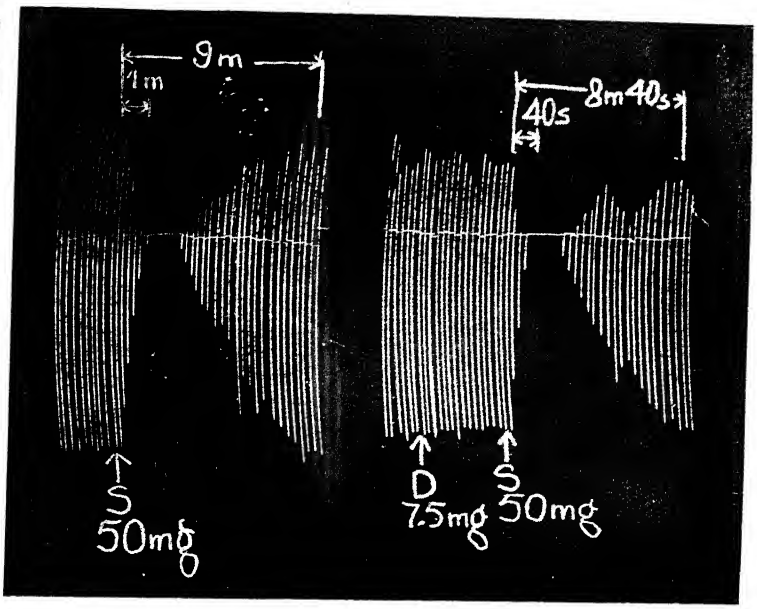


Fig 6a Showing the influence of diazepam on the neuromuscular blockade activity of succinylcholine (diazepam given 3-5 min before succinylcholine).

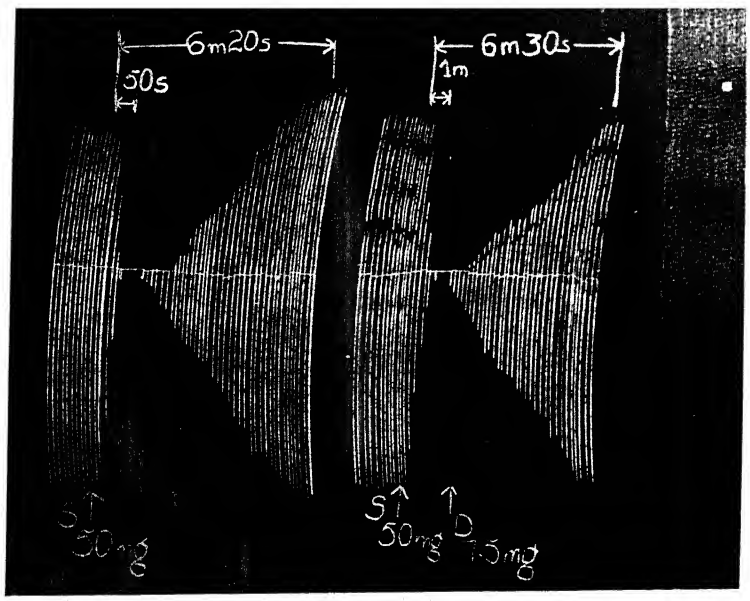


Fig 6b Showing the influence of diazepam on the neuromuscular blockade activity of succinylcholine (diazepam given at the start of recovery).

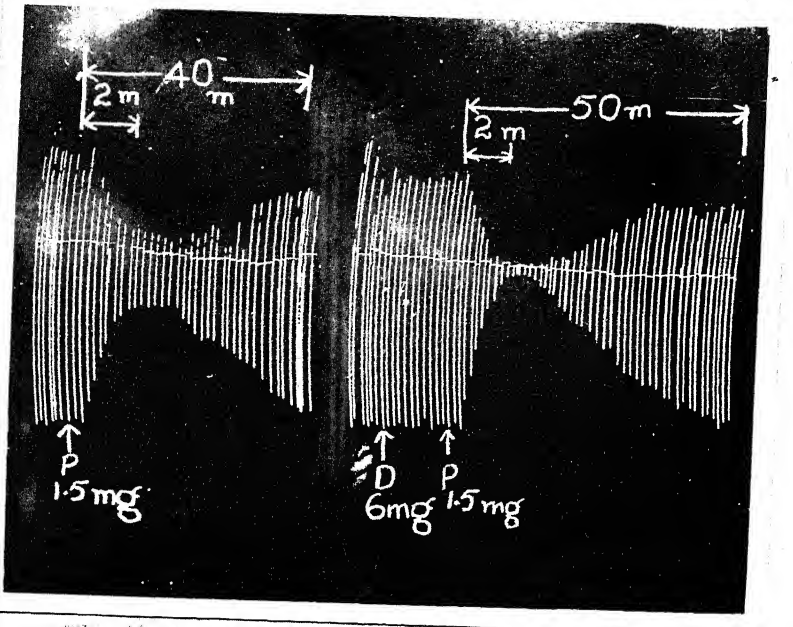


Fig 8a Showing the influence of diazepam on the neuromuscular blockade activity of pancuronium (diazepam given 3-5 min before pancuronium).

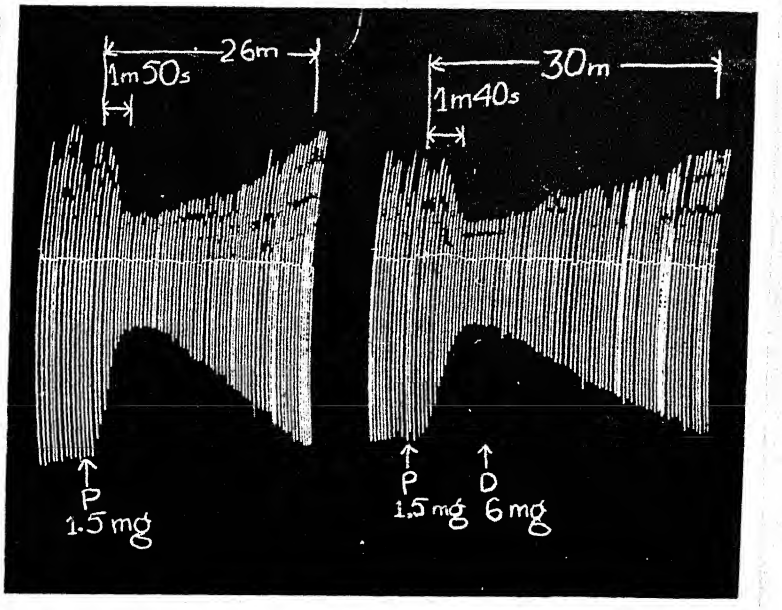


Fig 8b Showing the influence of diazepam on the neuromuscular blockade activity of pancuronium (diazepam given at the start of recovery).

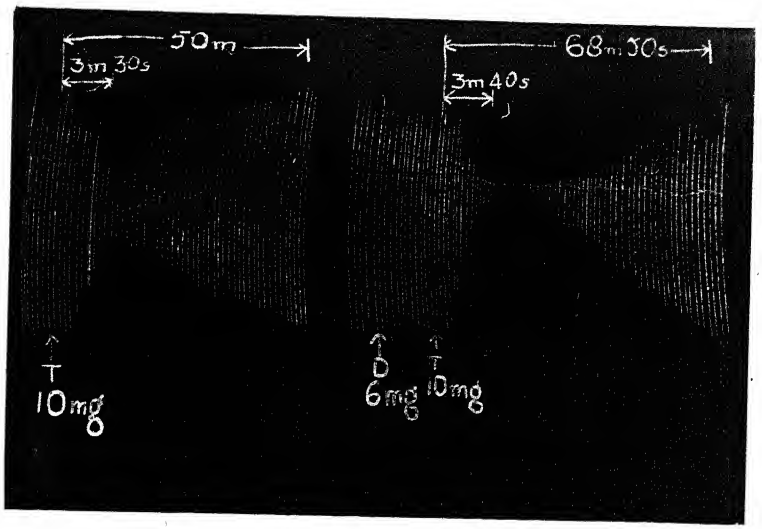


Fig 9a Showing the influence of diazepam on the neuromuscular blockade activity of tubocurarine (diazepam given 3-5 min before tubocurarine).

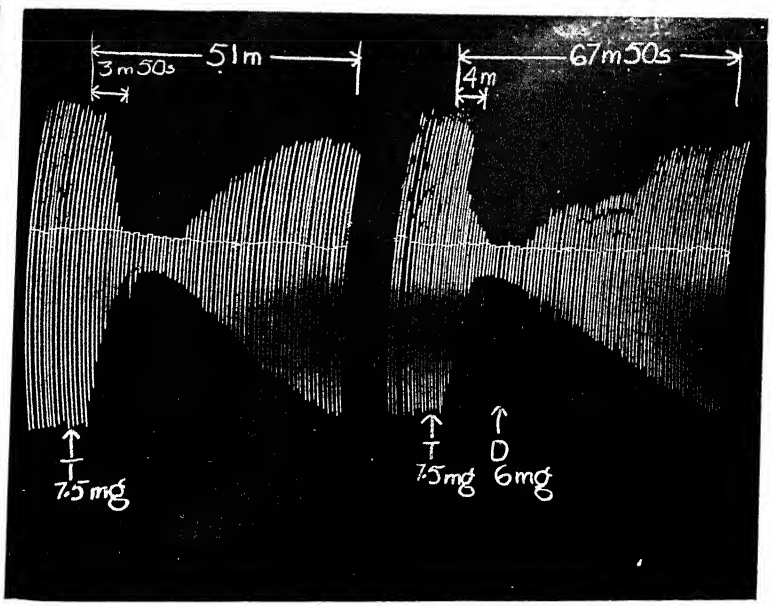
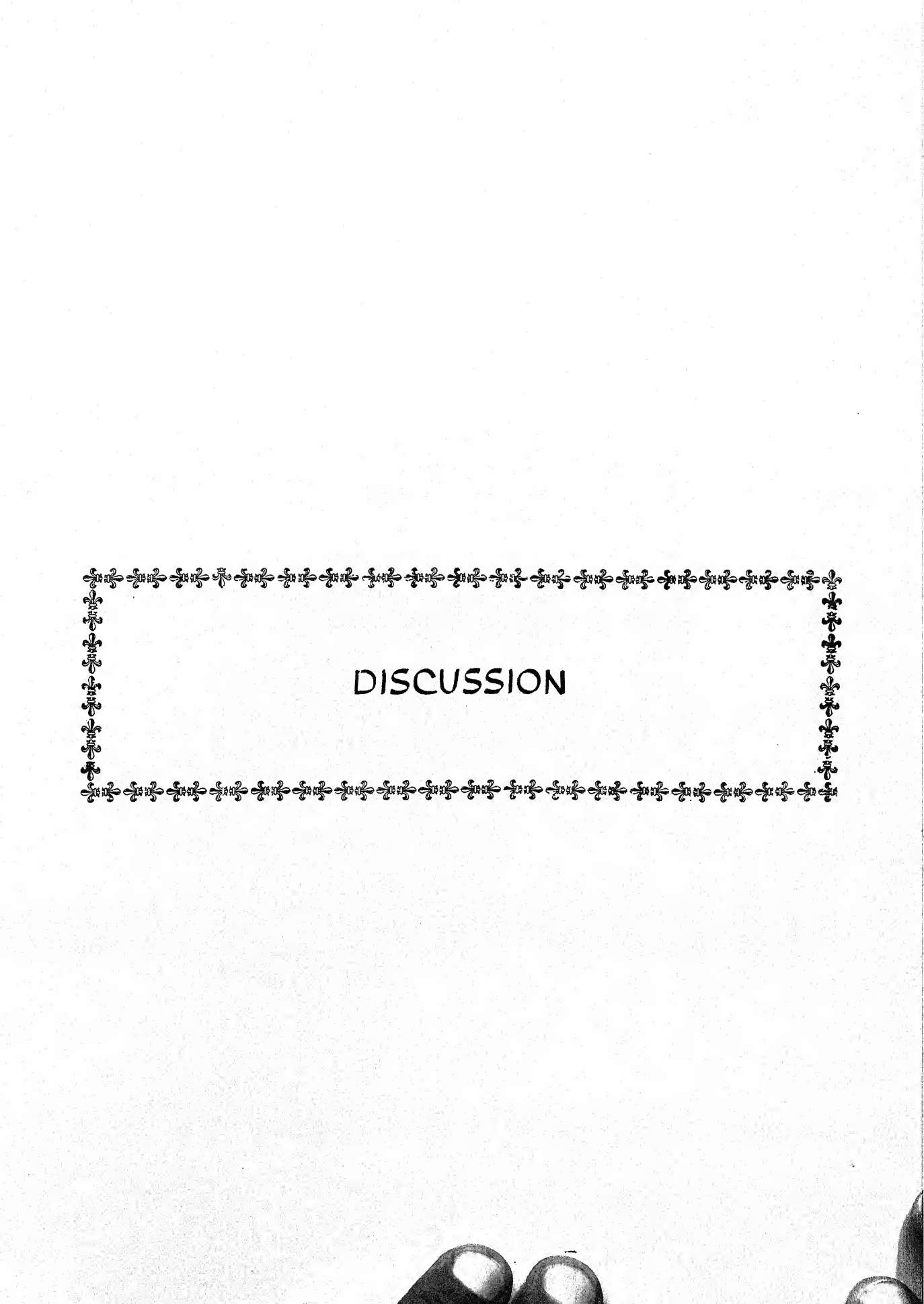


Fig 9b Showing the influence of diazepam on the neuromuscular blockade activity of tubocurarine (diazepam given at the start of recovery).

To assess the muscle relaxant property of diazepam, its effect was observed on twitch height in response to electrical stimulation in the 31 patients who received diazepam before muscle relaxant. It was observed that diazepam, when given alone, did not produce any alteration in the twitch height.

No difficulty was faced during the reversal from non-depolarising muscular blockade and none of the patient included in the study experienced any respiratory insufficiency post-operatively.

DISCUSSION



DISCUSSION

When one considers the many types of chemical compounds used in modern therapeutics, it is not surprising that some of these modify the action of muscle relaxants. In general such substances may interfere with neuromuscular transmission or may influence relaxants by actions at other sites. Some such side effects are well known. Others based on animal experiments on many different species and under varying conditions, are more difficult to assess precisely. Nevertheless, it would be unwise for anaesthetist to ignore the possible risk they suggest.

Diazepam is one of the most commonly used drugs in anaesthesia. It is used for a number of purposes like premedication and induction. Diazepam undoubtedly possesses a muscle relaxant property. Doughty (1970) reported a patient who received 10 mg of diazepam intravenously and developed apnoea with muscular relaxation for two hours ! For this muscle relaxant activity

both central (Ngai et al.,1966) and peripheral (Ludin and Dubach, 1971) sites of action have been suggested. Hence there is a probability that if diazepam is given along with muscle relaxants, it might influence their neuromuscular blocking action. There seems to be a considerable difference of opinions concerning the influence of diazepam on the action of muscle relaxants as is evident from the foregoing. A number of workers who conducted the investigations in this field arrived at different conclusions and still controversies surround this problem.

The present study was conducted on the patients presenting themselves at M.L.B. Medical College Hospital, Jhansi for various ailments requiring surgical intervention. Patients of ASA grade I and II only were included. Patients of ASA grade III, IV and V were spared as the severe systemic diseases are known to alter the patient's response to muscle relaxants.

The solution of diazepam is irritant, therefore, it was given only in large vein to prevent the occurence of thrombosis.

Halothane was used as and when needed in low concentrations. Katz and Gissen (1967) have reported that inhalation of 1-2% halothane does not cause any decrease in the twitch height response to ulnar nerve stimulation.

In the earliest studies the methods to observe the effects of muscle relaxant drugs were based on the clinical observations, grip strength measurements in conscious volunteers and tidal volume studies in anaesthetised patients. None of these methods proved entirely satisfactory.

Till today the only satisfactory method of determining the degree of neuromuscular block is to stimulate a motor nerve with an electric current and observe or record the contraction of muscle innervated by that nerve. The respiratory muscles themselves are difficult to test, but the hand muscles are readily accessible in most patients. Such muscles are particularly valuable because they are more 'sensitive' to the relaxants than the respiratory muscles, becoming paralysed earlier and staying paralysed longer (Churchill Davidson, 1965). The mechanical twitch height of adductor pollicis muscle provides an excellent guide to the

degree of relaxation produced by muscle relaxant drug (Katz, 1965). Therefore, in this study, the degree and duration of neuromuscular block produced by muscle relaxants were measured by recording the adduction movement of thumb (produced by contraction of adductor pollicis muscles) on a smoked paper in response to stimulation of ulnar nerve at wrist by a nerve stimulator. Sterile 24 gauge steel hypodermic needles were used as subcutaneous electrodes. The subcutaneous electrodes were preferred over surface electrodes as it is difficult to maintain a constant position with latter and skin necrosis may occur due to pressure of surface electrodes if used for prolonged periods (Katz, 1965; de Jong, 1966). The intensity of stimulus was adjusted in each case to get sufficient height of curve. The height of twitch response obtained is the function of muscle tension developed. Although this method provides rather a crude record, but once the twitch response of constant amplitude is obtained, it provides an accurate and reliable record of responses to neuromuscular blocking drugs (Baraka, 1964).

Muscle relaxants

Tubocurarine :

Its onset of action (218 ± 9.17 sec) and duration of action (46.87 ± 2.52 min) both were found to be longest as compared to other muscle relaxants studied. The onset of action of tubocurarine is significantly longer than gallamine ($P < 0.01$) and pancuronium ($P < 0.01$) (Table 8). Its duration of action also is significantly longer than gallamine ($P < 0.01$) and pancuronium ($P < 0.01$) (Table 9). Tubocurarine produced a mean twitch suppression of 76 ± 9.97% in doses of 0.21 ± 0.04 mg/kg and it is not significantly different from the degree of neuromuscular blockade produced by gallamine and tubocurarine (Table 10).

Different workers have observed different onset and duration of action of tubocurarine. Kats and coworkers (1969) found significantly different duration of action at London and New York. The onset of action of tubocurarine observed in the present study is comparable to those reported by Laurence (1975) and Sheth and Nabnis (1982). Various workers have reported its duration of action in a range of

30-50 min (Katz and Gissen, 1967 ; Bhargava and Chatterjee, 1977 ; Atkinsen et al., 1977 ; Feldman, 1978). The duration of action observed in the present study is within this range. A shorter duration of action (31.12 ± 11.60 min) was reported by Sheth and Sabnis (1982). Its onset as well as duration of action are significantly longer than pancuronium as reported by McDowall and Clarke (1969). The duration of action of tubocurarine was found to be 1.5 times longer than gallamine. Waltz and Dillon (1968) also obtained similar results.

Gallamine triethiodide :

The onset of action of gallamine (152.5 ± 6.42 sec) was found to be in between those of tubocurarine and pancuronium. Its differences from pancuronium ($P < 0.05$) and tubocurarine ($P < 0.01$) were statistically significant (Table 8). The duration of action of gallamine was shortest (31.43 ± 1.55 min) of all the non-depolarising muscle relaxants. Although the difference between duration of action of gallamine and pancuronium was statistically not significant, it was significant between gallamine and tubocurarine

($P < 0.01$)(Table 9). Gallamine produced a mean twitch suppression of 73.13 ± 6.17% with doses used in the study (Table 10).

The onset of action observed in the present study is in accordance with Monks (1972) who found it to be 2-4 min. Its duration of action is reported to be in a range of 20-40 min (Feldman, 1978 ; Snow, 1978 ; Sheth and Sabnis, 1982) and our observations comapre favourably with them.

Waltz and Dillon (1968) and Calvey and Wilson (1980) concluded that its speed of onset is greater than that of tubocurarine and its duration of action shorter. We also reached the same conclusion.

Pancuronium bromide :

The onset of action of pancuronium was found to be shortest (128.75 ± 6.89 sec). It is significantly shorter than gallamine ($P < 0.05$) and tubocurarine ($P < 0.01$) (Table 8). The duration of action of pancuronium came to be 34.46 ± 1.13 min which is significantly shorter than tubocurarine ($P < 0.01$) but the difference between pancuronium and gallamine was not significant (Table 9). In the doses

used in study it produced a mean twitch suppression of 75.63 ± 5.02% (Table 10).

The onset of action observed in the present work compares favourably with the workers who reported it in a range of 2-3 min (Bhargava and Chatterjee, 1977 ; Atkinson et al., 1977 ; Snow, 1978). The duration of action of pancuronium is reported to be in a range of 25-45 min (Varma and Sharma, 1971; Vickers et al., 1978 ; Atkinson et al., 1977 ; Snow, 1978 ; Feldman, 1978) and our results are within this range. The onset and duration of action of pancuronium were found to be shorter than tubocurarine which is in accordance with the observations of McDowall and Clarke (1969) and Feldman (1978).Contrary to this Sheth and Sabnis (1962) reported that the duration of action of pancuronium is longer than tubocurarine.

Succinylcholine :

The mean onset of action of succinylcholine was found to be 54 ± 3.51 sec (Table 8) and mean duration of action 7.61 ± 0.45 min (Table 9). It produced 100% twitch suppression with the doses used in the study (Table 10).

The onset of action observed in the present study is in accordance with Snow (1978) who stated that relaxation results within one min. The duration of action of succinylcholine was found to be within 5-15 min by various other workers (Crul et al., 1966 ; Snow, 1978 ; Calvey and Wilson, 1980; Blitt and coworkers, 1981) and our observations are within this range.

In the present study the effect of diazepam on neuromuscular blockade produced by muscle relaxants was observed in the same patient in whom the normal duration of action of that muscle relaxant was assessed. This method reduced error that would have been caused by individual variation. Feldman and Crawley (1970 b) using the same technique reported that it was not possible to demonstrate a cumulative effect with gallamine in doses used if more than 15 min were allowed to elapse between recovery from one dose of the drug and administration of the next.

The patients were divided into two groups. One group received diazepam (0.15 mg/kg iv) 3-5 min before giving muscle relaxant (Group A) and the other group received the same dose of diazepam at the start of recovery from neuromuscular blockade (Group B).

In group A we observed that the mean onset of action of the muscle relaxants namely succinylcholine, gallamine, pancuronium and tubocurarine, when diazepam was not used, was 57 ± 5.98 sec, 151.25 ± 12.01 sec, 126.25 ± 5.95 sec and 200.0 ± 14.94 sec respectively, whereas when the diazepam was used the mean onset of actioncame to be 50 ± 4.72 sec, 177.5 ± 10.97 sec, 128.75 ± 5.49 sec and 230 ± 14.81 sec respectively. Although there appears to be difference in our observations after diazepam pretreatment but it is not statistically significant (Table 12).

Our results are in conformity with Jain and coworkers (1976) who also failed to observe any effect of diazepam on the onset of action of tubocurarine in humans and of tubocurarine and gallamine in dogs.

It was observed that in group B (Table 13) the mean onset of action of succinylcholine, gallamine, pancuronium and tubocurarine came to be 51 ± 3.79, 153.75 ± 5.65, 131.25 ± 12.87 and 228 ± 10.18 sec respectively when diazepam was not used. On using diazepam at the start of recovery from muscle

relaxant activity the mean onset of action came to be 49.0 ± 2.34, 160.0 ± 7.07, 132.5 ± 12.20 and 242.0 ± 7.33 sec respectively. The difference observed in this group was also statistically not significant.

In this group diazepam was used when recovery from muscle relaxant activity started, as such it can not have any effect on the onset of action. As similar results were seen in group A also it can be logically inferred that diazepam does not influence the onset of action of these muscle relaxants.

In our series while observing the influence of diazepam on the duration of action of muscle relaxants in group A (Table 14), it was observed that after diazepam pretreatment although duration of action of succinylcholine was reduced from 7.70 ± 0.44 to 7.01 ± 0.41 min, but this was not statistically significant. In case of non - depolarising muscle relaxants, namely gallamine, pancuronium and tubocurarine, when diazepam was used their duration of action increased by 46.97%, 65.06% and 40.03% respectively which was significant

i.e. to say that there occurred a significant one and a half times increase in the duration of action of non-depolarizing muscle relaxants.

Our results are in conformity with Cheymol and coworkers (1967) who observed that the diazepam potentiated the effects of tubocurarine and gallamine, but did not interfere with the effects of succinylcholine. Same conclusion was also drawn by Sansone and coworkers (1967) using tubocurarine and Vergano and coworkers (1970) using tubocurarine and gallamine. Our results compare favourably with the workers who in their studies concluded that diazepam permits a considerable reduction in curarization during general anaesthesia. (Blondeau, 1964, 1965 a, b ; Stovner and Endresen, 1965 b ; Campan and Espagno, 1966). Feldman and Crawley (1970 a,b) observed that diazepam increased the duration of block produced by gallamine by three folds. Stovner and colleagues (1971) found that after using diazepam the doses of pancuronium and gallamine were reduced by 7-8%.

In the present study we failed to observe any significant alteration in the duration

of action of succinylcholine by diazepam and it compares favourably with the earlier reports (Stovner and Endresen, 1965a ; Tonsa, 1966 ; Bradshaw and Maddison, 1979 ; Southgate and Wilson, 1971).

In group B (Table 15) there was also decrease in duration of action of succinylcholine from 7.51 ± 0.80 to 6.68 ± 0.50 min, when diazepam was given at the start of recovery, but it was not statistically significant. In case of non-depolarizing muscle relaxant namely gallamine, pancuronium and tubocurarine the duration of action increased by 52.47%, 43.44% and 35.02% respectively and this increase was statistically significant.

In the present series, the degree of muscular blockade was assessed by measuring the twitch suppression produced by muscle relaxants. In group A (Table 16) it was observed that, succinylcholine (given in doses of 1 mg kg^{-1}) caused 100% twitch suppression when either diazepam was given before the muscle relaxant or it was not given at all. While with the non-depolarizing muscle relaxants namely gallamine, pancuronium and tubocurarine there was increase of twitch suppression by 31.29%,

27.64% and 28.57% respectively when the diazepam was used. This increase in case of non-depolarising muscle relaxants is significant.

Our results compare favourably with those of Feldman and Crawley (1970a, b) who observed a three fold increase in the degree of blockade produced by gallamine with diazepam, Vergano and coworkers (1970) using tubocurarine and gallamine and Jain and coworkers (1976) who used gallamine.

In group B (Table 17) also the twitch suppression produced by succinylcholine was 100% irrespective of fact whether diazepam was given at the time of start of recovery or not. While when diazepam was given at the time of starting of recovery from muscle relaxant activity of gallamine, pancuronium and tubocurarine there was slight increase in the twitch suppression as compared with that when diazepam was not used (from 74.38 $\pm$ 8.73 to 81.25 $\pm$ 7.24 %, 74.38 $\pm$ 6.08 to 81.25 $\pm$ 6.46 % and 75.0 $\pm$ 8.64 to 79.0 $\pm$ 9.52 % respectively). This increase is statistically not significant, and can be explained due to the cumulative effect of the first dose of the muscle relaxants.

In the present study it was observed that diazepam alone produced no effect on the twitch height of adductor pollicis muscle in response to electrical stimulation of ulnar nerve. It was also observed in the various clinical (Feldman and Crawley, 1970 a, b; Bradshaw and Maddison , 1979)and experimental studies (Webb and Bradshaw, 1973; Jain and coworkers, 1976).

Therefore in the present study we observed that after giving diazepam there occurred a significant increase in the duration of action as well as the degree of blockade produced by non-depolarising muscle relaxants namely gallamine, pancuronium and tubocurarine while the duration of action of succinylcholine remained unaffected. This increase could have been caused by diazepam, which possesses an undisputable muscle relaxant property. Feldman and Crawley (1970 a, b) concluded that diazepam influenced the action of muscle relaxants by inhibiting presynaptic release of acetylcholine. Few other workers also suggested a peripheral site of action (Hamilton, 1967; Dretchen et al., 1971; Ludin and Dubach, 1971; Hopf and Dillman, 1973). But in the present study

we observed that diazepam alone did not affect the twitch height, therefore, it can be concluded fairly that diazepam does not possess any peripheral action. Most of the workers, who investigated the site of action of diazepam are also of the opinion, that diazepam exerts muscle relaxant activity by acting at a site other than peripheral. Supraspinal structures, such as reticular activating system and polysynaptic pathways in the spinal cord have been considered as the probable sites of action accounting for muscle relaxation produced by diazepam (Randall and coworkers, 1961; Ngai et al., 1966; Webb and Bradshaw, 1973; Bradshaw and Maddison, 1979). Zbinden and Randall (1967) who studied its muscle relaxant property in dystonic - athetoid children with cerebral palsy, contributed it to its anti-anxiety effect. However, the clinical experience of Marsh (1965) and Howard (1963) indicates that at least part of its beneficial effect is due to a pharmacological action on polysynaptic pathways within spinal cord or on supraspinal structures.

We, like Feldman and Crawley (1970 b), observed that there occurred potentiation of the effect of non-depolarizing muscle relaxants after giving diazepam when the muscle relaxants were

administered 15 min after recovery from the effect of first dose. This could have been due to cumulative effect of the first dose of non-depolarizing muscle relaxant (tubocurarine, pancuronium and gallamine) as the workers like Webb and Bradshaw (1973) have observed marked cumulative effect persists even if the dose interval is 30 min to 1 hour apart.

Contrary to this Feldman and Crowley (1970 b) had reported that there is no cumulation of effect when the dose is repeated 15 min after recovery from first dose.

It appears to us that the potentiation observed in the present study is not alone due to effect of diazepam but also due to cumulative effect as one can not deny the fact that there is cumulative effect of second dose of drug even if it is administered at the interval of 30 min to 1 hour (Webb and Bradshaw, 1973).

There is controversy regarding the site of action of diazepam and we have found that it does not have any peripheral action. The potentiation of effect of non-depolarizing muscle

relaxants indicates that diazepam should have site of action other than peripheral. Martins (1975) also arrived at a similar conclusion. If this be the case then there should also be potentiation of the effect of depolarising muscle relaxant like succinylcholine, which was not observed by us. This can be explained by the fact that there had been masking of the effect of diazepam due to tachyphylaxis with subsequent doses of succinylcholine (It was the third dose of succinylcholine in the same patient on which the influence of diazepam was studied as the first dose was administered to facilitate the endotracheal intubation and second dose served as control). Tachyphylaxis has also been reported by Crul and coworkers (1966).

In view of the foregoing, it is evident that the diazepam potentiates the action of non-depolarising muscle relaxants but it is not very marked. Therefore, diazepam can be used safely with the muscle relaxants. However, it should be kept in mind that this potentiation may be dangerously aggravated in certain pathological conditions or if the diazepam is used in very high doses.

CONCLUSION

C O N C L U S I O N

After carefully analysing the observations, obtained in the series of 62 patients studied in the present work, we concluded that

1. The onset and duration of action of tubocurarine were 218 ± 9.17 sec and 46.87 ± 2.52 min respectively.

2. The onset and duration of action of gallamine were 152.5 ± 6.42 sec and 31.43 ± 1.55 min respectively.

3. The onset and duration of action of pancuronium were 128.75 ± 6.89 sec and 34.46 ± 1.13 min respectively.

4. The onset and duration of action of succinylcholine were 54 ± 3.51 sec and 7.61 ± 0.45 min respectively.

5. Among non-depolarising muscle relaxants studied in the present work pancuronium acted most rapidly and the tubocurarine was slowest with gallamine in between.

6. The duration of action of tubocurarine was significantly longer than that of gallamine

and pancuronium while difference between the latter two was not significant.

7. Diazepam did not affect the onset of action of any of the muscle relaxant studied in the present work.

8. The observed potentiation of duration of action and degree of blockade produced by non-depolarising muscle relaxants after giving diazepam might be partly due to diazepam, by virtue of its muscle relaxant property, and partly due to cumulative effect of first dose of muscle relaxant.

9. The duration of action of succinylcholine was not altered, whether the diazepam was given before it or at the start of recovery from its action. This might have been due to masking of potentiating effect of diazepam by tachyphylaxis.

10. The site of action of diazepam is not peripheral accounting for its muscle relaxant property.

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